DYNAMIC ^{1}H NMR AND ELECTRON SPECTROSCOPY OF SOME CYCLIC OXAMIDES, THIOOXAMIDES AND α-DIKETONES

Experimental studies and theoretical calculations

ROLAND ISAKSSON

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Abstract

Syntheses of some five-,six-, and seven-membered cyclic oxamides and some of their monothio and dithio analogues have been presented.

Conformations and free energy barriers to inversion of N,N'-dialkylperhydrodiazepine-2,3-dione and its monothio and dithio analogues have been studied by ^{1}H NMR spectroscopy and by molecular mechanics calculations.

Photoelectron spectra of five-,six-, and seven-membered cyclic oxamides in which the oxamide unit is forced to adopt an s-cis or twisted s-cis conformation have been recorded. The spectra have been interpreted using ab initio calculations.

A series of dithiooxamides with dihedral angles of ca 90°, 65° and 30° between the thioamide chromophores have been studied by ultraviolet photoelectron and absorption spectroscopy.

Finally, the dynamic stereochemistry of some seven-membered cyclic α-diketones have been investigated by ^{1}H NMR spectroscopy and by molecular mechanics calculations.

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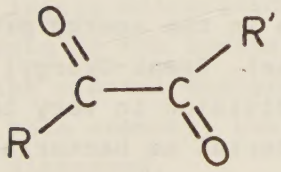
BACKGROUND

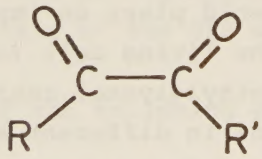
Since long time α-dicarbonyl compounds have been paid much interest by spectroscopists and theoreticians. The reason for that interest is found in the unusual electronic properties of this class of compounds. Two strong dipoles, the carbonyl units, are brought close to each other, resulting in a strong electronic interaction. It is also found that this interaction is very sensitive to substituents and to conformational parameters.[1]

The intramolecular torsional potentials and barriers to rotation around the pivot bond of the carbonyls of simple α-diketones, such as glyoxal and biacetyl, have been studied intensively by various spectroscopic methods combined with calculations on different levels of approximation (CNDO, INDO, MINDO and ab initio).[2-5] One reason for that interest has been an attempt to obtain an estimate of the steric and electronic contributions to the rotational barriers.[2] Another reason for the investigations has been the problem of the stereochemistry of compounds, containing the CO-CO unit.

Both planar s-cis and s-trans (see below) conformers of α-diketones should be stabilized by partial π-bonding, and as far as glyoxal[3] is concerned both conformers have also been detected experimentally. The s-cis conformer of biacetyl could not be detected, probably due to the strong steric repulsion between the methyl groups in the molecule.[4]



s-trans



s-cis

The magnitude of the dipole-dipole repulsion of the two carbonyls in α-diketones depends on the dihedral angle between them. This repulsion has its maximum value for the planar s-cis conformation and decreases with an increasing dihedral angle. The interaction of these dipoles influences both the conformational and electronic properties of this class of compounds.

The energy splitting between the molecular orbitals is a measure of the extent of orbital interaction by "through bond" or "through space" interaction mechanism.[6] Electronic spectra of α-diketones[7] show that the "through bond" mechanism dominates both in s-cis and s-trans compounds.

Much less studied than the α-diketones are oxamides and their mono and dithio analogues. These compounds exhibit many of the properties of the α-diketones. Oxamides are also interesting from the biological point of view, as they may be considered as two amides brought to bonding distance in the same molecule. Also in this class of compounds a strong relationship exists between absorption properties and structure.[8]

The use of α-diketones in photochemical reactions is known since at least 1886[10] and several reviews[9,10] have appeared in the literature. As α-diketones have absorption at longer wavelengths than most organic compounds including their products of reactions, they have commonly been used as simple light absorption filters in photochemical experiments. The energy absorbed can be transferred to other molecules and induce chemical reactions.

The α-diketones are also important from the synthetical point of view. These compounds provide a basis for obtaining aliphatic, aromatic and heterocyclic products. Synthesis of α-diketones has been reviewed.[11]

Oxalic acid plays an important role in the energy production of the living cell (citrate cycle). Szent-Gyorgyi[12] has found that methylglyoxal inhibits cell division in very low concentrations in different kinds of material as bacteria, frog cells, normal and cancerous cells.

THE PURPOSE OF THE THESIS

The purpose of this thesis is primarily to study the conformational properties and to investigate the electrostatic and steric contributions to the inversion barriers of some cyclic seven-membered oxamides and some of their mono and dithio analogues. In this molecular system the dicarbonyl unit is forced to adopt a twisted conformation. Inversion of the ring system should involve a passage of the (thio)carbonyl groups in a planar s-cis arrangement with maximum electrostatic interaction, making it possible to obtain information on the steric and electrostatic properties of this dicarbonyl arrangement.

Some seven-membered cyclic α-diketones were included in the study to allow comparisons with a more fundamental α-dicarbonyl system. The following techniques have been used in the study.

Dynamic ^{1}H NMR technique was used to obtain the free energies for the inversion process of the seven-membered rings.

Molecular mechanics calculations[13] were carried out to aid the interpretation of the barriers to inversion in terms of steric and electrostatic interactions. Two different electrostatic models, dipole-dipole and charge-charge interaction, were used. These calculations were also used to solve conformational problems.

Ultraviolet photoelectron spectroscopy (UPS) was introduced to investigate the possibility to obtain conformational information for the cyclic (thio)oxamides by this technique.

Ultraviolet spectroscopy (UV) was introduced as a complement to the other studies in analyzing the electronic properties of these compounds.

Ab initio calculations were carried out to enable the assignments of the ionization potentials of the UPS and to obtain the orbital energies.

In this summary, the contents of the following papers will be discussed.

I. Synthesis of Some Five-, Six-, and Seven-membered Cyclic Oxamides and Their Mono and Dithio Analogues.
R. Isaksson, T. Liljefors and J. Sandström, J. Chem. Research (S), 1981, 43; J. Chem. Research (M), 1981, 664.

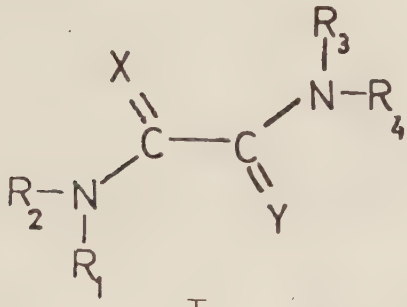
II. Conformations and Barriers to Inversion of Seven-membered Cyclic Oxamides and their Monothio and Dithio Analogues. A Study by Dynamic NMR Spectroscopy and Molecular Mechanics.
R. Isaksson and T. Liljefors, Accepted for publication in J. Chem. Soc. Perkin Trans. II.

III. Ab initio Calculations and Photoelectron Spectra of Cyclic Oxamides.
R. Isaksson and T. Liljefors, J. Chem. Soc. Perkin Trans. II, 1980, 1815.

IV. Ultraviolet Absorption and Photoelectron Spectra of Some Cyclic and Open-chain Mono- and Dithiooxamides.
L. Henriksen, R. Isaksson, T. Liljefors and J. Sandström, Submitted to Acta Chem. Scand. B.

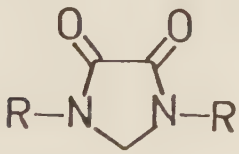
V. Conformations and Barriers to Inversion of Some Seven-membered Cyclic α-Diketones. A Study by Dynamic NMR Spectroscopy and Molecular Mechanics Calculation.
R. Isaksson and T. Liljefors, Manuscript.

Table 1. (Thio)oxamide Compounds Studied in This Thesis.



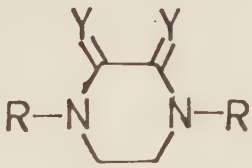
I

I	X	Y	R_1	R_2	R_3	R_4
a	O	O	H	H	H	H
b	O	O	Me	H	Me	H
c	O	O	Me	Me	Me	Me
d	S	S	Me	H	Me	H
e	S	S	Me	Me	Me	Me
f	S	O	Me	Me	H	H
g	S	O	H	H	Me	Me



II

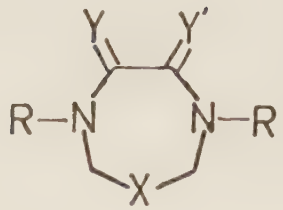
a) R=H
b) R=Me



III

a) R=H, Y=O
b) R=Me, Y=O
c) R=H, Y=S
d) R=Me, Y=S

Table 1. (contd.)



IV

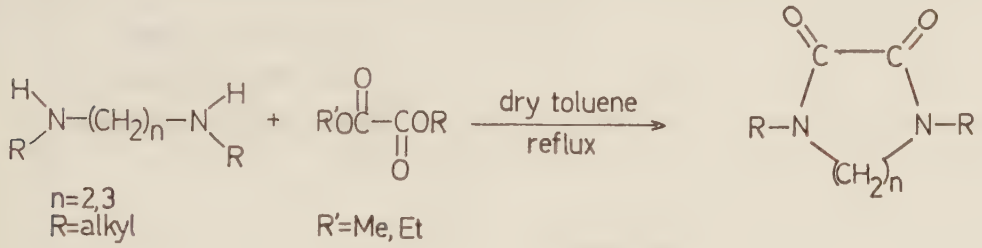
IV	R	X	Y	Y'
a	H	CH_2	O	O
b	Me	CH_2	O	O
c	Et	CH_2	O	O
d	i-Pr	CH_2	O	O
e	$PhCH_2$	CH_2	O	O
f	$PhCH_2$	$C(Me)_2$	O	O
g	i-Pr	$C(Me)_2$	O	O
h	$PhCH_2$	CH_2	O	S
i	i-Pr	CH_2	O	S
j	i-Pr	CH_2	S	S
k	$PhCH_2$	CH_2	S	S
l	$PhCH_2$	$C(Me)_2$	S	S
m	Me	CH_2	S	S

Synthesis of Cyclic Oxamides and Their Mono and Dithio Analogues (Paper I)

This part of the thesis very briefly describes the synthesis of the five- (II), six- (III) and seven-membered (IV) cyclic oxamides and some of their mono and dithio analogues.

The emphasis is on the seven-membered ring system, which according to calculations[14] has geometrically rather unperturbed (thio)amide units. The five- and six-membered rings were prepared to obtain variation of the dihedral angle between the carbonyl units.

The preparations of the six- and seven-membered rings III and IV were carried out according to the scheme below.

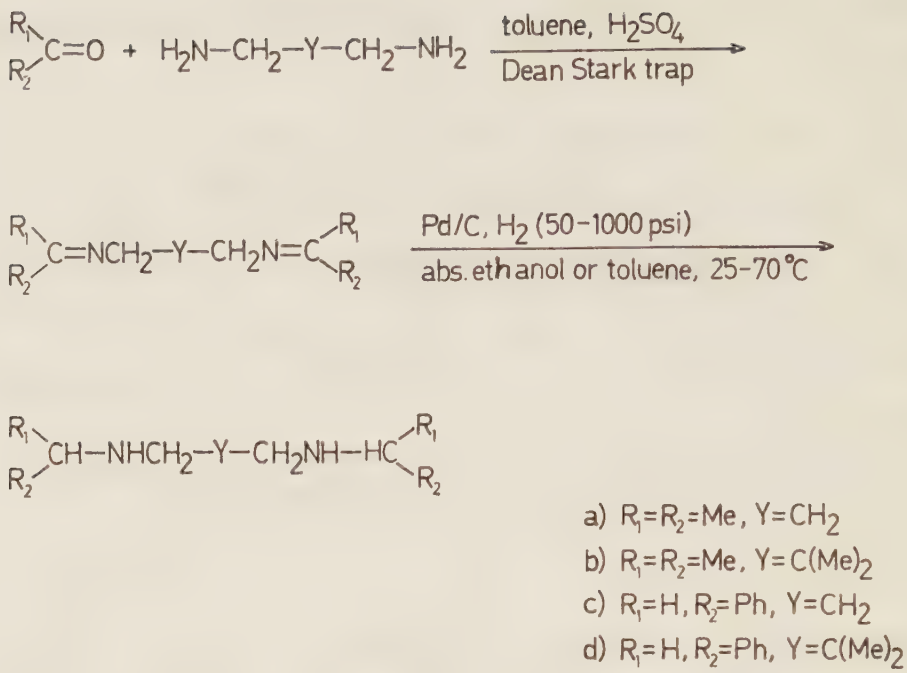


The monothio and dithio analogues IIId and IVh-m were prepared using p-methoxyphenylthioxophosphine sulphide[15] as thionation agent. High yields of either the mono or dithio compounds were obtained under relatively mild conditions by using a slight excess of the reagent, 1.1 or 2.2 eq. respectively.

All N,N'-dialkyl-1,3-diaminopropanes, except for the N,N'-diethyl compound,[16] were prepared by condensation reactions between acetone or benzaldehyde and the primary 1,3-propanediamines, yielding the Schiff bases as isolable intermediates. The secondary diamines were finally obtained by catalytic hydrogenations (Pd on carbon as catalyst) in an autoclave using ethanol or toluene as solvent. Hydrogen pressures were varied from 50 to 1000 psi. See Scheme 1 on next page.

All attempts to prepare compounds IIa, IIIc and IVa failed.

The N,N'-disubstituted compound IIb was isolated in an anodic bis-acetoxylation reaction of N,N,N',N'-tetramethyloxamide (Ic). The five-membered ring was isolated from the destilled



a) $R_1=R_2=Me$, $Y=CH_2$
b) $R_1=R_2=Me$, $Y=C(Me)_2$
c) $R_1=H$, $R_2=Ph$, $Y=CH_2$
d) $R_1=H$, $R_2=Ph$, $Y=C(Me)_2$

Scheme 1.

reaction mixture as crystals in low yields, less than 10 %. The five-membered ring IIa could not be isolated but was detected in the mass spectroscopical analyses of the evaporated reaction mixture. This compound seems to exist in an equilibrium mixture with an open form compound, which made the attempts of isolation and purification unsuccessful. A similar reaction has been reported earlier.[17]

Conformational Analysis of the cyclic (thio)oxamides IVd-f and IVh-l. (Paper II).

The experimental ^{1}H NMR spectra of the compounds IVd-f and IVh-l are described in detail in Paper II and in Table 2. These spectra indicate that the four methyls of IVd and IVj and the four benzylic methylene protons of IVe,f,k,l are pair-wise equivalent or enantiotopic in the ground state conformation of the molecules. Only conformations that have a C_2 axis or a

Table 2. 1H NMR data at slow exchange.

Compd. IV	Signals studied	Solvent	Temp/K	$\Delta\nu$/Hz	J_{CH_3-CH}/Hz	J_{AB}/Hz
d	$CH(\underline{CH_3})_2$	$CHCl_2F$	204.2	5.9	6.8 6.8	– –
e	$Ph-\underline{CH_2}-$	$CDCl_3$	198.9	33.2		13.7
f	$Ph-\underline{CH_2}-$	$CDCl_3$	215.1	152.7		
	$-C(CH_3)_2-\underline{CH_2}-$			39.5		15.5
h	$CH(\underline{CH_3})_2$ [a]	$CDCl_3$	285.4	6.5	6.7 6.7	
	$CH(\underline{CH_3})_2$ [b]			7.5	7.1 7.1	
i	$Ph-\underline{CH_2}$ [a]	$CDCl_3$	253.5	33.4		14.3
	$Ph-\underline{CH_2}$ [b]			26.8		14.2

Table 2. (contd.)

Compd. IV	Signals studied	Solvent	Temp/K	$\Delta\nu$/Hz	J_{CH_3-CH}/Hz	J_{AB}/Hz
j	$CH(\underline{CH_3})_2$	Isoquinoline	429.2	7.2	6.7 6.7	
k	Ph-$\underline{CH_2}$	Isoquinoline[c]	375.0	20.6		14.4
l	Ph-$\underline{CH_2}$	Isoquinoline[c]	409.4	194.6		14.2
	$-C(CH_3)_2-\underline{CH_2}-$			41.9		14.4

[a] Amide unit.

[b] Thioamide unit.

[c] HMSO as reference.

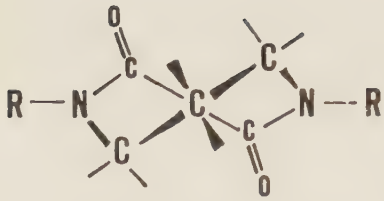
mirror plane through the ring system bisecting the bond between the two (thio)carbonyls can be consistent with these spectra.

High barriers to rotation around the C-N bond in amides and thioamides have been reported in several investigations.[18] The main reason for that is π-conjugation in the amide unit, which due to this conjugation prefers a planar or almost planar conformation. This rigidity of the (thio)amide units in the seven-membered systems studied restricts the conformational freedom of the compounds and thus to some extent simplifies the analyses. It was found that the three low energy conformations with symmetries C_2, C_s and C_1 (shown below) found for 1,3-cycloheptanediene[19] were appropriate as models for the seven-membered (thio)amides. The π-bonds of the 1,3-cycloheptanediene keep the ethylene units of this molecule planar and thus restrict the conformational freedom in the same way as the π-conjugation of the (thio)oxamide units does.

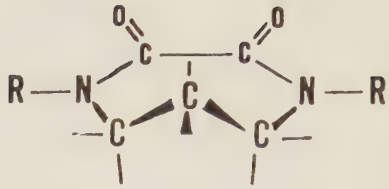
Other conformations such as twist - chair, chair or boat all require considerable twisting around the amide C-N bonds and could thus be excluded.

The geminal methyl groups of compounds IVf and IVl show only a sharp singlet at all temperatures studied. This is in agreement with a conformation with C_2 symmetry. The C_2 twist boat was calculated to be 9-20 kcal/mol lower in energy than the C_s conformer, and the C_1 conformer was only 2 kcal/mol lower in energy than the C_s conformer. It was also found that the C_2 conformer in contrast to the others represents a local minimum on the potential energy surface.

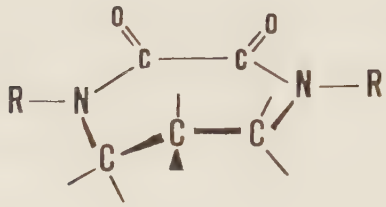
The dihedral angles between the (thio)carbonyl groups were calculated to be 60-65°, with the higher values for the sulphur compounds.



C_2



C_s

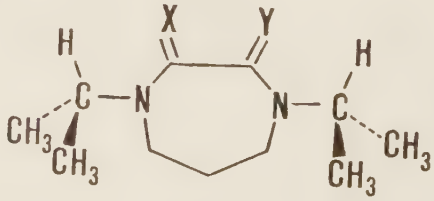


C_1

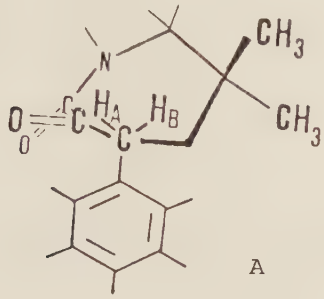
The conformations of the N-alkyl groups

The ^{1}H NMR spectra also provided information about the conformations of the N-alkyl substituents.

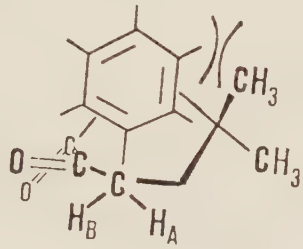
The chemical shifts of the methine protons of compounds IVd,g,j are δ 4.77, 5.67 and 5.67 ppm, respectively. These resonance frequencies indicate that the methine protons are in or close to the amide plane and pointing towards the (thio)-carbonyl group.[20,21] Molecular mechanics calculations also resulted in lower energies for a conformation having the methine proton in the (thio)amide plane and pointing towards the (thio)-carbonyl group. The preferred conformation is shown below.



The N-benzyl compounds IVe,f,h,k,l may have two non-equivalent approximately perpendicular conformations shown in the figure below. The fast interchange between these sites reduces $\Delta\nu_{AB}$ to the greatest extent in compounds IVe,h,k (see Table 2). In compounds IVf,l the two geminal ring methyl groups interfere with the benzyl groups and leave one of these conformations (B) almost unpopulated, and as a result large $\Delta\nu_{AB}$ values are observed. These results are also supported by the molecular mechanics calculations.



A



B

Barriers to inversion in seven-membered (thio)oxamides

As can be seen in Table 3, the free energy barriers increase in the order oxamide, monothiooxamide and dithiooxamide. Similar results were obtained in a study of the acyclic tetrabenzyloxamide and its mono and dithio analogues by Carter and Sandström.[22] They found the corresponding barriers ($\Delta G^{\ddagger}$) to be 9.7, 17.6 and > 24 kcal/mol, respectively. Substitution of one oxygen with a sulphur atom of the acyclic compound increases the barrier with about 8 kcal/mol and substitution of both oxygen atoms with sulphur atoms increases the barrier with more than 16 kcal/mol. The corresponding values for the cyclic compounds are 5-6 kcal and 11-13 kcal/mol, respectively.

The barriers of the acyclic compounds[22] were interpreted in terms of steric interactions between the oxygen or sulphur in one half of the molecule and the benzylic methylene group in the other half in a planar s-trans transition state. The inversion barriers for the cyclic (thio)oxamides reflect steric and electrostatic interactions between two (thio)-carbonyl groups in a planar s-cis transition state. The simi-

Table 3. Free energy barriers to inversion.

Compound IV	$\Delta G^{\ddagger}$ [a] (kcal/mol)	Temp (K)
d	11.1[b]	208.8
e	10.7	202.9
f	12.0	215.1
h	17.2	298.6
i	15.7	284.4
j	24.1	447.6
k	23.3	431.5
l	23.2	409.4

[a] Estimated error ± 0.1 kcal/mol. The rate constants were obtained from visual fittings of experimental to calculated spectra and the free energies at appropriate temperatures from the Eyring equation.

[b] $\Delta H^{\ddagger}$ = 10.0 ± 0.1 kcal/mol, $\Delta S^{\ddagger}$ = -5.2 ± 0.7 cal/mol. deg, only random errors calculated from the standard deviations in the Eyring plot are included.

larity of the thermodynamic parameters is therefore somewhat unexpected.

To be able to analyze the experimental barrier heights in terms of electrostatic and steric interactions, molecular mechanics calculations were carried out. The C_s conformer mentioned above was found to be a local maximum on the potential energy surface and could be used as a model for the transition state. Two different methods of calculating the electrostatic interactions, dipole-dipole and charge-charge models were used. The atomic charges were obtained from CNDO/2 calculations.[14]

The results from the calculations are shown in Table 4. In the table the electrostatic part of the barrier is included to obtain a better picture of the different contributions to

Table 4. Molecular mechanics calculated inversion barriers and experimental $\Delta H^{\ddagger}$.

Compound IV	Calc. barrier (kcal/mol)		Electrostatic part of the barrier (kcal/mol)	Exp. $\Delta H^{\ddagger}$ [c] (kcal/mol)
d	DI [a]	13.7		10.0
	CH [b]	10.3	0.7	
e	DI	11.5		9.6
	CH	8.8	1.2	
f	DI	12.2		10.9
	CH	9.7	1.1	
h	DI	15.7		15.6
	CH	13.4	1.1	
i	DI	13.6		14.2
	CH	12.2	1.9	
j	DI	21.6		21.8
	CH	19.9	1.6	
k	DI	19.2		21.1
	CH	19.4	3.3	
l	DI	19.6		21.1
	CH	18.9	2.3	

[a] DI = dipole interaction model. [b] CH = charge interaction model.

[c] The free activation enthalpies were evaluated from the free activation energies in Table 3 and the activation entropy found for compound IVd.

the barriers. The experimental differences in barriers between oxamides, monothiooxamides and dithiooxamides are satisfactorily reproduced by the calculations, best with the charge-charge model. In spite of the planar arrangement of the two (thio)-carbonyls in the transition state (C_s conformer) and an expected increase in dipole-dipole (charge-charge) interaction compared to the initial state (C_2 conformer), the electrostatic contribution, according to the calculations, is less than 20 % of the total inversion barrier. An explanation for the surprisingly small electrostatic contribution to the barriers is found in the dihedral angle between the two (thio)carbonyls. In the initial state the dipole-dipole/charge-charge repulsion already has a considerable magnitude, due to the small CO-CO angle, about 60°.

In the passage through the planar s-cis conformation the $C(sp^2)$-$C(sp^2)$-N angle increases according to the calculations about 13° and the O=C-N angle decreases about 9° compared with the corresponding angles of the ground state. These angle bendings give as a result an increase in the steric energy.

It should be noticed that the cyclic (thio)oxamides are chiral molecules. The high barriers of the dithio compounds should make it possible to resolve them in enantiomers. Mannschreck and coworkers[23] have separated tetramethyldithiooxamide Ie in enantiomers and they found the barrier to racemization to be 25.6 kcal/mol.

Photoelectron Spectra of Some Cyclic Oxamides (Paper III)

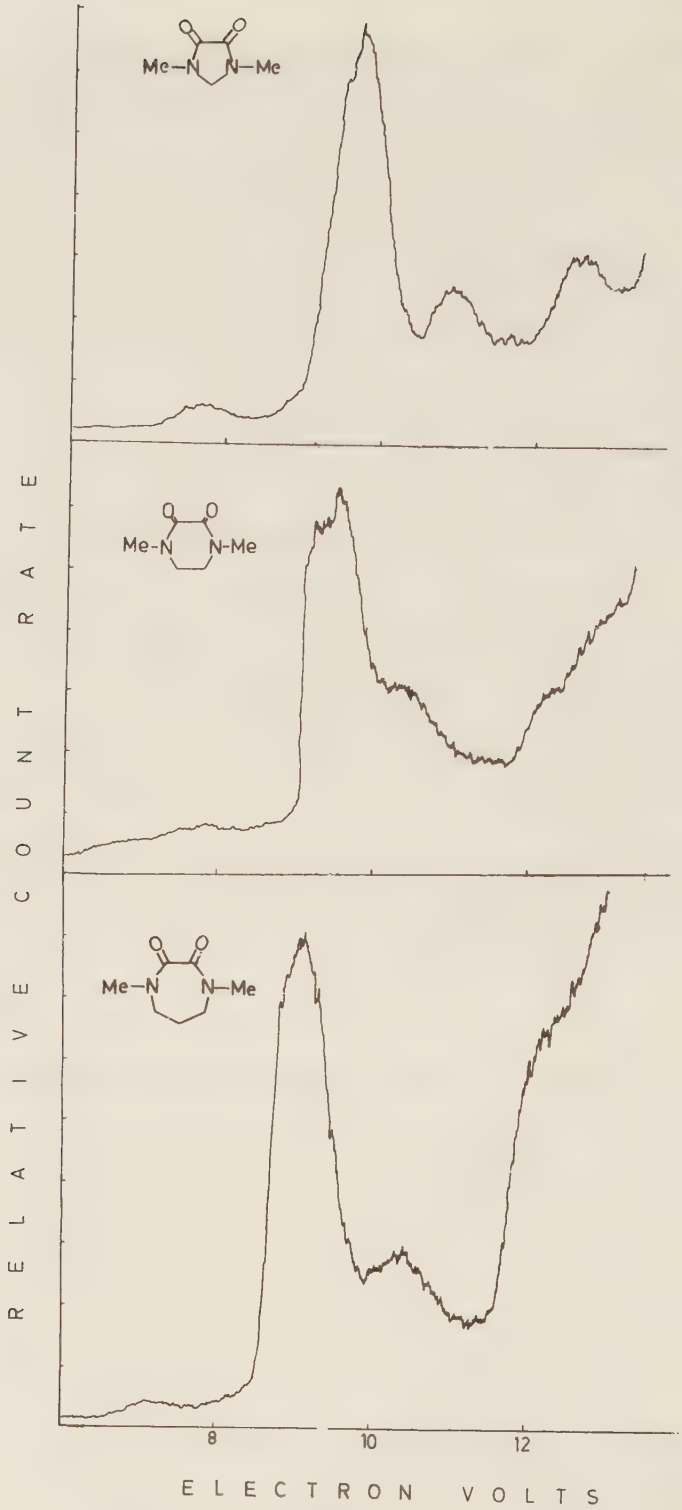
Ultraviolet photoelectron spectroscopy (UPS) has been successfully used for systems having lone pairs on vicinal atoms, to obtain conformational information of the molecules.[24] The ionisation potentials (IP) have been correlated with geometrical parameters, such as dihedral angles between the lone pairs. The interaction between orbitals results in splittings of energy levels and occurs generally "through bond" or "through space". For "through space" interaction it is necessary that the orbitals are in such relative spatial positions that significant overlap between them may occur. The "through bond" interaction on the other side refers to coupling between

two orbitals by virtue of their mutual symmetry that allows interaction with a third orbital. It is found that the "through space" interactions are small compared to the "through bond" interactions[25] for this class of compounds.

Earlier oxamide (Ia) and some of its derivatives, all s-trans or twisted s-trans, have been studied by UPS.[26] These investigations have mainly been concerned with assignments of IP:s and with effects of N-alkylations,[27,28] not specifically with studies of conformations or correlations of IP;s conformational properties of the molecules.

In this thesis the oxamide unit was incorporated in rings of different sizes, five- (II), six-, (III) and seven- (IV) membered rings to obtain s-cis or twisted s-cisoid conformation to allow comparisons with s-trans or twisted s-transoid molecules of the same class. The CO-CO dihedral angle could thus be varied from ca 0° for the five-membered ring to ca 20° and ca 60° for the six- and seven-membered rings, respectively. The estimates of the dihedral angles for six- and seven-membered rings were obtained from the molecular mechanics calculations.

The UPS spectra of the N,N'-dimethyl-substituted five-, six-, and seven-membered rings are shown on page 18.


Me–N
N–Me
Me-N
N-Me
Me–N
N–Me
RELATIVE COUNT RATE
8
10
12
ELECTRON VOLTS

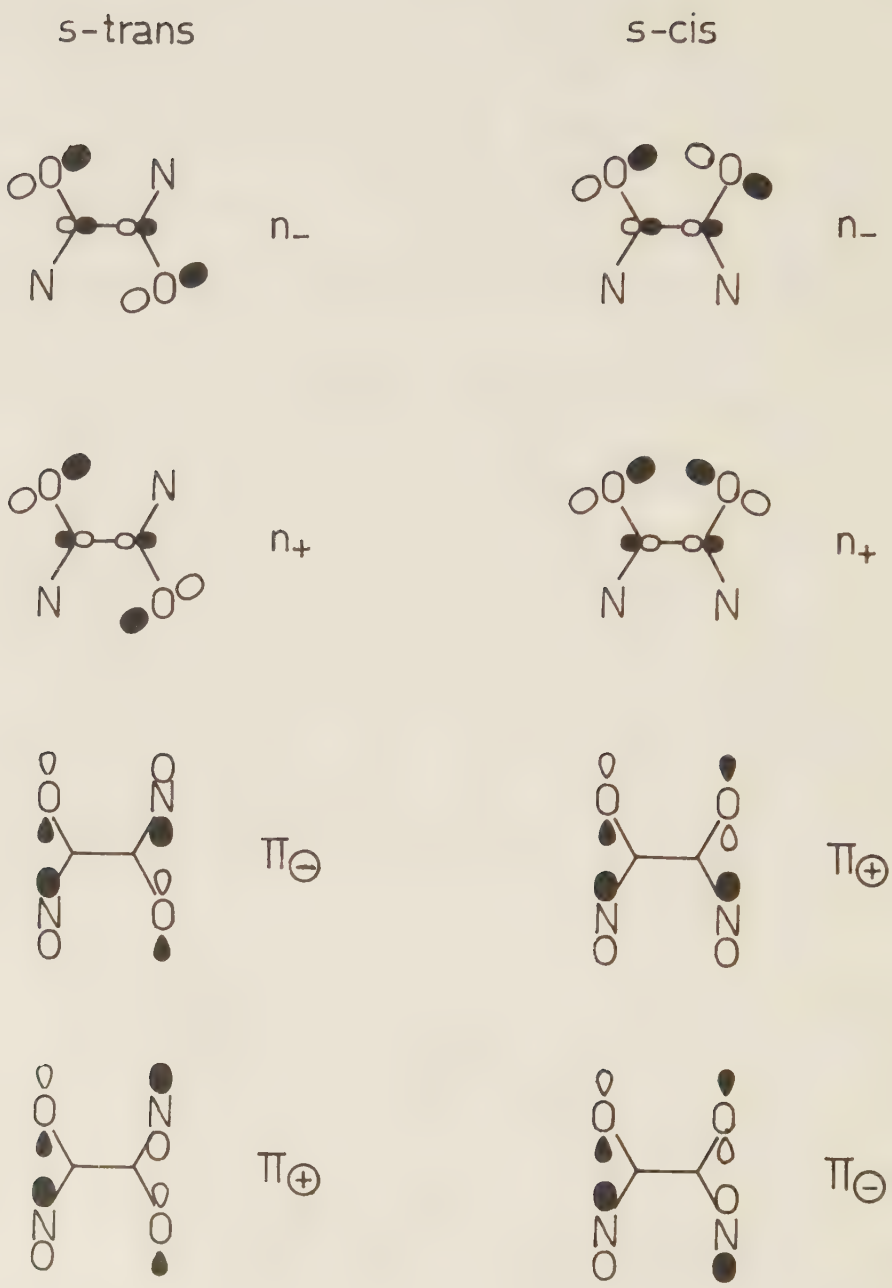
The lack of fine structure in the spectra made it difficult to perform the proper assignments without use of calculations. In the assignments for the cyclic compounds studied, ab initio calculations were employed and empirical corrections for reorganization and correlation effects were introduced. The acyclic tetramethyloxamide (Ic) was included in the investigation to allow comparisons with the cyclic compounds.

All calculations except for compound Ib were performed for N-unsubstituted parent compounds. In Scheme 2 below the calculated MO:s of interest, with the nomenclature suggested by McGlynn,[26] are shown.

To the negatives of the orbital energies (ε_j) of the unsubstituted compounds were added empirical corrections, obtained as the difference between calculated energies for the four highest occupied orbitals in s-trans oxamide and the observed experimental ionisation energies. Furthermore, the experimental N,N'-dimethylation[28] shifts of McGlynn were added, taking the $\pi_{\oplus}/\pi_{\ominus}$ inversion of the s-cis compounds into account. Together, all these corrections to the calculated MO:s of, for instance, s-trans oxamide (Ia) reversed the orbital ordering in the predicted spectrum compared to the ordering in the calculated MO:s of the ground state. It must, therefore, be taken into account that the introduction of correction terms may alter the ordering of the MO:s obtained from the calculations, or, expressed otherwise, the ordering of MO:s and IP:s does not need to be the same.

It was found from calculations that the N-alkyl shifts are composites of changes in MO energies and changes in reorganization and correlation energies. The correction terms derived from UPS and ab initio calculations could be used without modifications in the assignments of the unsubstituted six-membered oxamide (IIIa).

A comparison between the unsubstituted six-membered s-cisoid oxamide (IIIa) and N,N'-dimethyloxamide (Ib), a s-trans compound, was carried out to see to what extent the IP:s were influenced by geometrical changes. Alkyl bridging is a common method to lock molecules in certain conformations. It was found that the observed IP:s depend both on conformational differences and on effects due to differences between N-methy-



Scheme 2.

lation and alkyl bridging.

Summarizing the results of this part of the thesis: *Ab initio* calculations together with correction terms, obtained from experiments, reproduce the experiments (IP:s) satisfactorily. To extract conformational information from UPS is not always straightforward as many effects are involved when modifications of geometries are made by, for instance, alkyl bridging.

UPS and UV of Some Cyclic Thiooxamides (Paper IV)

Thiooxamides have commonly been used by spectroscopists as models for amides, due to their generally well separated energy levels with lower energies than the corresponding amides. UV and UPS spectra of these compounds may yield valuable information that can be used in the interpretation of the spectra of the biologically more interesting amides.

This part of the thesis was carried out to make comparisons with oxamides concerning orbital energies (IP:s), alkylation effects, transition energies (UV), and conformational properties.

It was found that the assignments of the IP:s of the thio compounds were easier to perform, due to a somewhat better separation between the ionisation bands in the spectra. The interaction of perturbation, due to the greater energy gap between the n and highest π-orbitals on one hand and the C-C orbitals of the skeleton on the other, is of less importance in the dithiooxamides than in oxamides. Simple perturbation arguments can be used to further facilitate the assignments of the IP:s.

The more "isolated" thioamide chromophore also facilitates the analyses of the correlation between IP:s and conformations, as it was possible to separate the effects from alkylations and geometry changes.

The assignments of the IP:s of N,N'-dimethyldithiooxamide (**Id**) are very illustrative to the above mentioned discussion. Adding the alkylation shifts[28] alone inverts the order between the IP:s compared to tetramethyldithiooxamide (**Ie**).

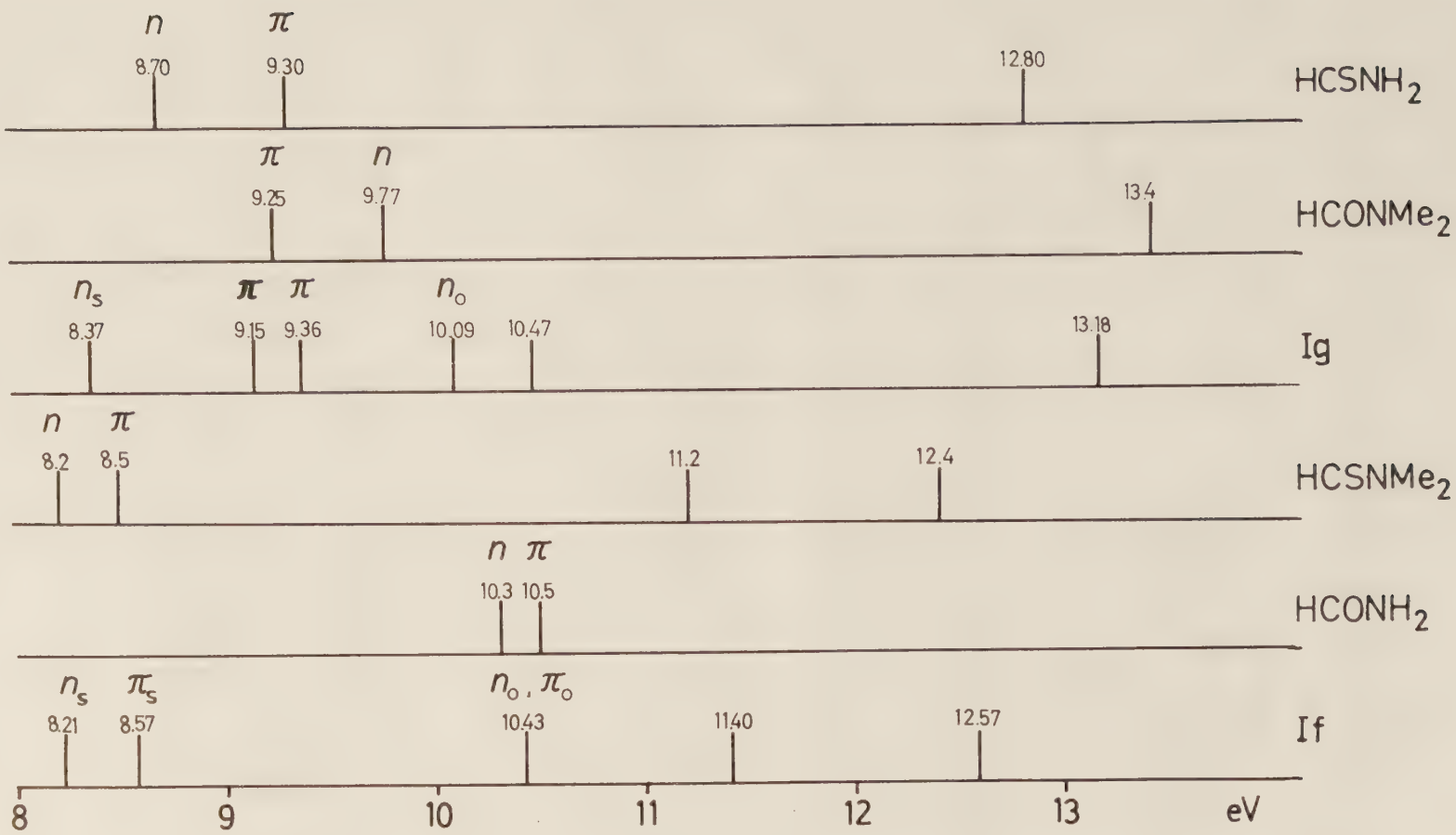
However, adding the effects of the changes in dihedral angles between the thioamide units on the MO energies,[29] results in the same ordering of the IP:s as for Ie.

This sensitivity to changes of the dihedral angles was also found in a comparison of the six- and seven-membered rings. The $\pi_{\ominus}$ and n_{-} (see Scheme 2) energies were inverted and the n_{+} and $\pi_{\oplus}$ levels decreased with the reduction of the dihedral angle.

In the monothiooxamides the n and π levels have different energies in the two halves of the molecules and a much weaker interaction should be expected. The UPS of N^{O},N^{O}-dimethylmonothiooxamide (Ig) and N^{S},N^{S}-analogue (If) could be well reproduced by adding the UPS of thioformamide and N,N-dimethylformamide and the UPS of N,N-dimethylthioformamide and formamide, respectively (Scheme 3). Deviation from additivity is smallest for compound If where the differences in energy are largest, as expected. The same was found for the cyclic monothiooxamide IVi . The experimental data are found in Paper IV.

The influence of substitution as well as of conformational changes, on the electronic states of the UV spectrum is generally more readily analyzed than the influence of the corresponding factors on the IP:s of the UPS. One important reason for that is that the electronic states are all affected to almost the same extent by such perturbations. In the UPS, however, the IP:s are more irregularily perturbed and for that reason are also more difficult to interpret.

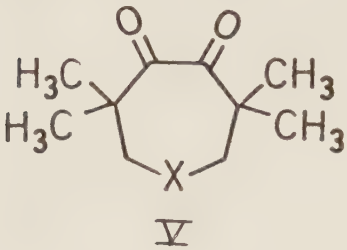
To achieve conformational information from either UV or UPS spectra it seems as if the spectra of mono- and dithiooxamides are easier to analyze than the corresponding spectra of oxamides. It was also found that the UV spectra were more clear-cut to interpret than the UPS spectra.


n
π
8.70
9.30
12.80
HCSNH2
π
n
9.25
9.77
13.4
HCONMe2
ns
π
π
no
8.37
9.15
9.36
10.09
10.47
13.18
Ig
n
π
8.2
8.5
11.2
12.4
HCSNMe2
n
π
10.3
10.5
HCONH2
ns
πs
no , πo
8.21
8.57
10.43
11.40
12.57
If
8
9
10
11
12
13
eV

Scheme 3.

Cyclic α-Diketones (Paper V).

In this part of the thesis the following compounds have been studied.



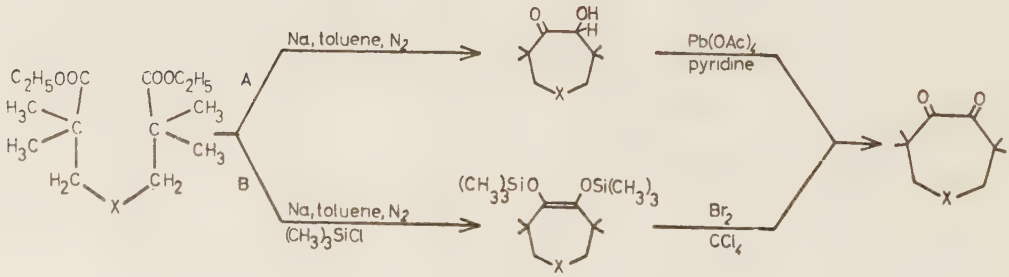
V

V	
a	X=CH_2
b	X=O
c	X=S
d	X=NCH_3
e	X=$NC(CH_3)_3$

The dynamic stereochemistry of compounds Va-e were studied by dynamic ^{1}H NMR spectroscopy and by molecular mechanics calculations. For the purpose of the calculations a force-field for α-dicarbonyl compounds was developed and added to the MMP1 molecular mechanics program developed by Allinger and coworkers[13,30].

Syntheses of the Cyclic α-Diketones Va-e.

Compounds Va-e were prepared according to the methods described by Johnson[31] and Wynberg[32]. Starting from the corresponding acyclic diester, the acyloin condensations and oxidation reactions were performed according to Scheme 4.



Scheme 4.

Compounds Vc-e were prepared according route A and Va-b according to B.

^{1}H NMR Spectra and Conformational Analysis of Va-e.

The ambient temperature ^{1}H NMR spectra of compounds Va-e display a sharp singlet for the four methylene groups and in Vb-e a sharp singlet for the ring methylene protons.At lower temperatures these signals broaden and split into a doublet for the methyl protons and AB quartets for the methylene protons,except for Vd and Ve where,due to small shifts and overlapping N-substituent signals,the analysis of the methyl and methylene resonance signals,respectively,was precluded.

The NMR spectra below coalescence are only consistent with conformations having C_s or C_2 symmetries,possibly time-averaged,with the methyl groups and methylene protons being pairwise equivalent or enantiotopic.

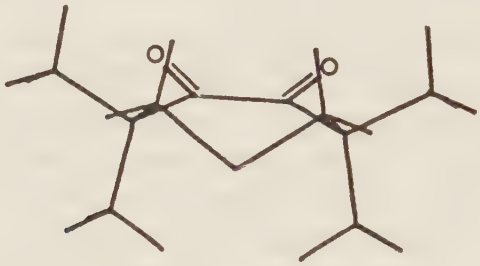
A large number of conformations of the seven-membered ring system are formally possible in analogy with the conformations on the pseudorotational pathways of cycloheptane[33].However, steric interaction between the methyl groups and electrostatic repulsion between the carbonyl oxygens significantly reduces the number of low energy conformations of Va-e.

Molecular mechanics calculations indicate the presence of only two low energy conformations, a distorted chair with C_1 symmetry and a C_2 twist-boat conformation.The calculated geometries of these conformers for Vc are shown on page 27 and the corresponding conformational energies for Va-e and the calculated carbonyl-carbonyl dihedral angles are given in Table 5.The carbonyl-carbonyl dihedral angle of Va,95°, as calculated by molecular mechanics method is in good agreement with conclusions drawn from UV-data,90-110°.[34] The dihedral angles for Va-e are calculated to be significantly larger than those calculated for the seven-membered cyclic oxamides IVa-g(ca. 60°).

The methyl groups and methylene protons in the C_1 conformation may be pairwise exchanged by a low energy pseudorotational process as shown on page 28. This exchange process leads to a time averaged C_2 symmetry in agreement with the appearance of the low temperature NMR spectra.
The barrier of this pseudorotational process is however too low to allow it to be ''frozen out'' in the NMR spectra.

Barriers to Inversion of α-Diketones Va-e.

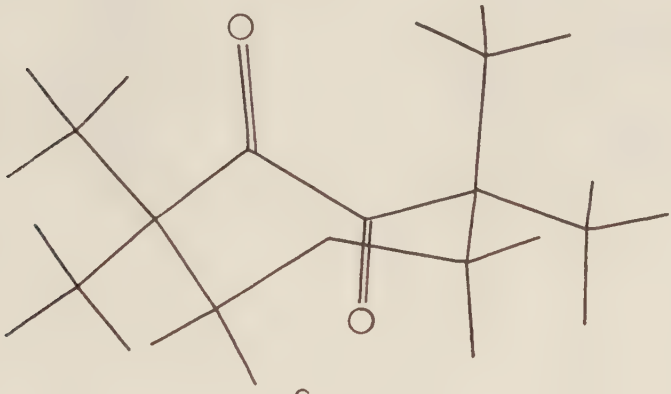
The experimental free energies of activation for the inversion of the seven-membered ring system in Va-e are given in Table 6.For Vc a complete bandshape analysis was performed.
Using the molecular mechanics method a C_s chair conformation with a planar s-cis dicarbonyl arrangement was found to be a suitable model for the transition state of the inversion process.



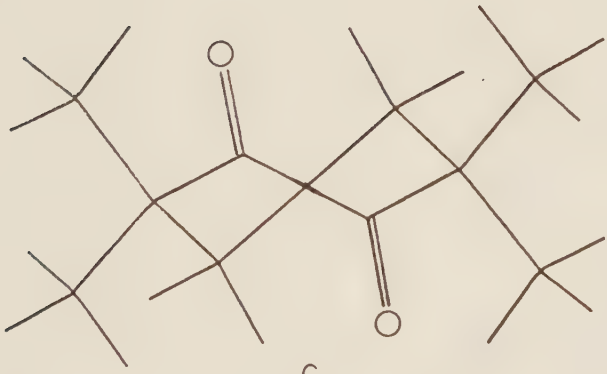
C_s

Calculated inversion barriers are given in Table 7.In the calculations two models for calculating the electrostatic interactions were used.No significant difference between the sets of calculated barriers was however found.The electrostatic part of the inversion barriers was calculated to be 36-58% of the total barrier heights, which is much larger than was calculated for the seven-membered cyclic oxamides, 7-14% (Table 4.). One reason for this difference may be found in differencies in the initial state carbonyl-carbonyl dihedral angles for the two series of compounds.

In the oxamide series dihedral angles were calculated to be ca. 60°, while the corresponding angles in system V are 90-114°. In the oxamide series there is thus a comparatively larger electrostatic repulsion present in the initial state of the inversion process.



C_1



C_2

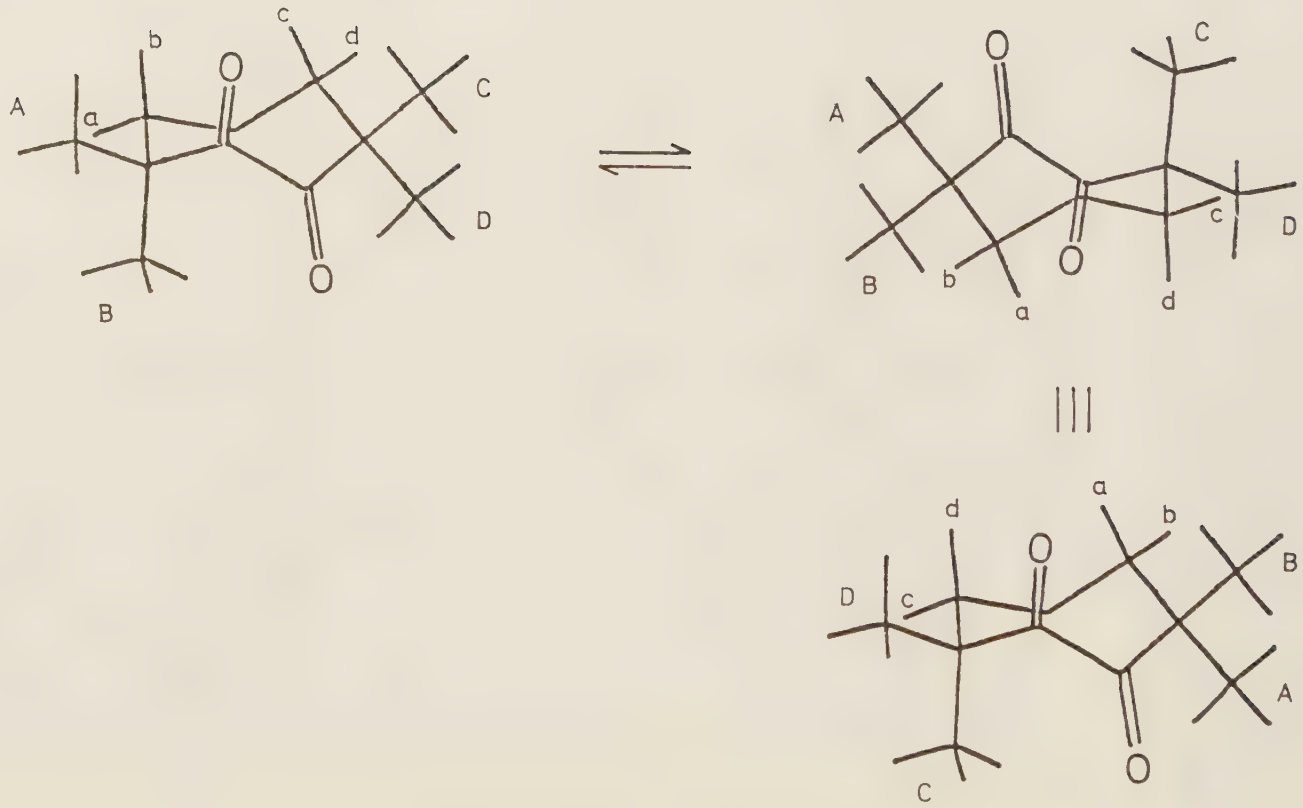

A
a
b
B
O
c
d
C
D
O
A
B
b
a
O
O
C
c
D
d
a
b
B
A
O
d
D
c
C
O

Table 5. Calculated conformational energies [a] and carbonyl-carbonyl dihedral angles for compounds V**a**-**e**.

Compound	C_1 conformation (kcal/mol)	CO-CO dihedral angle (deg.)	C_2 twist-boat (kcal/mol)	CO-CO dihedral angle (deg.)
V				
a	+ 1.05	103.8	0	94.5
b	0	99.6	+ 0.33	89.7
c	0	114.8	+ 0.82	105.4
d	0	101.0	+ 0.57	92.1
e	0	100.1	+ 4.18	90.4

[a] dipole approximation.

Table 6. Free energy barriers to inversion for compounds **V**a-e.

Compound	Signals studied	$\Delta G^{\#}$ (kcal/mol) [a]	Temp. (K)
V			
a	CH_3	8.7	168.0
b	CH_3	8.6	171.1
b	CH_2	8.6	171.1
c	CH_3	10.8[b]	171.0
c	CH_2	10.8[b]	211.9
d	CH_3	9.1	181.4
e	CH_2	9.3	186.0

a) estimated error ± 0.1 kcal/mol

b) ΔH = 10.8 ± 0.1 kcal/mol
ΔS = - 0.1 ± 0.3 cal/mol.deg

Only random errors calculated from the standard deviations in the Eyring plot are included.

Table 7. Molecular mechanics calculated inversion barriers[a)] for compounds **Va-e**.

Compound **V**	Dipole-dipole model		Charge-charge model	
	calc.barrier	electrostatic part	calc. barrier	electrostatic part
a	10.6	3.9	10.8	3.9
b	7.7	4.4	7.9	4.6
c	11.7	4.9	11.8	5.0
d	8.6	4.2	8.8	4.4
e	8.4	3.9	8.8	4.3

a) energies in kcal/mol

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PAPER I

Synthesis of Some Five, Six-, and Seven-membered Cyclic Oxamides and Their Mono- and Di-thio Analogues

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J. Chem. Research (M), 1981, 0664–0682

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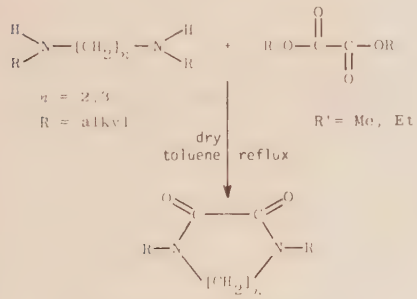
In connection with conformational studies of oxamides and their monothio and dithio analogues, we wish to be able to study the steric and electronic interactions in the s-*cis* and twisted s-*cis* conformations.[6] In order to make this possible we need to force the oxamide unit to adopt the desired conformation by the constraints of a ring system. So far only a few cyclic oxamides have been reported and to our knowledge none of their monothio and dithio derivatives.

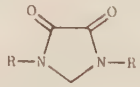
In this paper we report the syntheses of some five-, six-, and seven-membered cyclic oxamides as well as their monothio and dithio analogues [compounds (I)–(III)]. The emphasis is on the seven-membered ring system, which, according to models, is large enough to have only a small influence on the normal oxamide geometry, but still small enough to give the ring system some degree of rigidity. The five- and six-membered oxamides were prepared as examples with different dihedral angles of the intercarbonyl bond.

The six- and seven-membered ring compounds (IIa, b, d), and (IIIb–f) were prepared according to the following scheme:

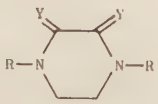


Compounds (IId) and (IIIh–m) were prepared using a new thionation reagent, *p*-methoxyphenylthioxophosphine sulphide.[7] This cheap and readily available reagent gave high yields (80–100%) of either dithio or monothio compounds under mild conditions depending on the amount of reagent used. Analytically pure compounds were obtained by preparative thin-layer chromatography.

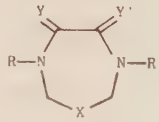
All *N,N'*-dialkyl-1,3-diaminopropanes used in the ring formation reactions except for the *N,N'*-diethyl[8] compound were prepared by condensation reactions between acetone or benzaldehyde and primary diamines. The secondary diamines were then obtained by hydrogenation in a Parr apparatus using ethanol or toluene as solvent under moderate to high hydrogen pressures (50–1000 lb in $^{-2}$). The catalyst used in all reactions was palladium on carbon (10%).



(I)a; R = H
b; R = Me



(II)a; R = H, Y = O
b; R = Me, Y = O
c; R = H, Y = S
d; R = Me, Y = S



	R	X	Y	Y'
(III)a	H	CH_2	O	O
b	Me	CH_2	O	O
c	Et	CH_2	O	O
d	Pr^i	CH_2	O	O
e	$PhCH_2$	CH_2	O	O
f	$PhCH_2$	CMe_2	O	O
g	Pr^i	CMe_2	O	O
h	$PhCH_2$	CH_2	O	S
i	Pr^i	CH_2	O	S
j	Pr^i	CH_2	S	S
k	$PhCH_2$	CH_2	S	S
l	$PhCH_2$	CMe_2	S	S
m	Me	CH_2	S	S

The five-membered rings (I) could not be prepared by the methods mentioned above. The *N,N'*-disubstituted compound (Ib) was isolated in an anodic bis-acetoxylation (large scale laboratory electrolysis) of *N,N,N',N'*-tetramethyloxamide.[11] The desired product slowly separates from the distilled reaction mixture. The yields are low (less than 10%).

References: 13

Table: Experimental data for compounds (I)–(III)

Paper: E/205/80

Received: 7th July 1980; revised version received on 20th November 1980

References cited in this synopsis:
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SYNTHESES OF SOME FIVE-, SIX-, AND SEVENMEMBERED CYCLIC OXAMIDES AND THEIR MONO AND DITHIO ANALOGUES

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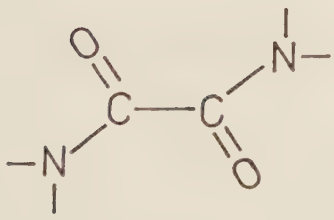
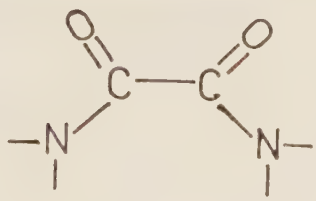
INTRODUCTION

Oxamides may adopt either the s-trans or the s-cis conformation. In the crystalline state oxamide[1] as well as dithio-oxamide[2] is planar s-trans, but in N-substituted derivatives steric interactions may prohibit the planar conformation and induce twisting around the carbonyl-carbonyl bond.



s-trans



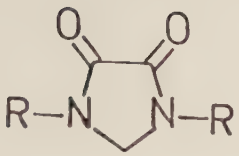
s-cis

N-Alkyl substituted oxamides are generally s-trans, but show an increasing degree of twisting with increasing N-substitution.[3] The tetraalkyl derivatives have a dihedral angle close to 90°, according to NMR[4] and dipole moment studies.[5] The s-cis conformation is in all cases insignificantly populated.

In connection with conformational studies of oxamides and their monothio and dithio analogues, we wish to be able to study the steric and electronic interactions in the s-cis and twisted s-cis conformations.[6] In order to make this possible we need to force the oxamide unit to adopt the desired conformation by the constraints of a ring system. So far only a few cyclic oxamides have been reported and to our knowledge none of their monothio or dithio derivatives.

In this paper we wish to report the syntheses of some five-, six- and seven-membered cyclic oxamides as well as their monothio and dithio analogues. The emphasis is on the seven-membered ring system which according to models is large enough to have only a small influence on the normal oxamide geometry (bond lengths and bond angles), but still small enough to give the ring system some degree of rigidity. Some five- and six-membered oxamides have also been prepared to allow variation of the dihedral angle of the intercarbonyl bond.

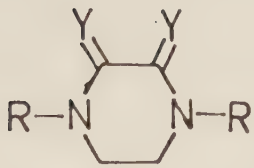
The compounds discussed in this paper are shown below.



I

a) R=H

b) R=Me



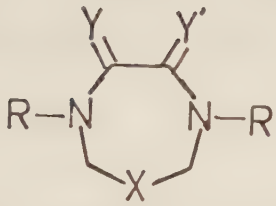
II

a) R=H , Y=O

b) R=Me, Y=O

c) R=H , Y=S

d) R=Me, Y=S



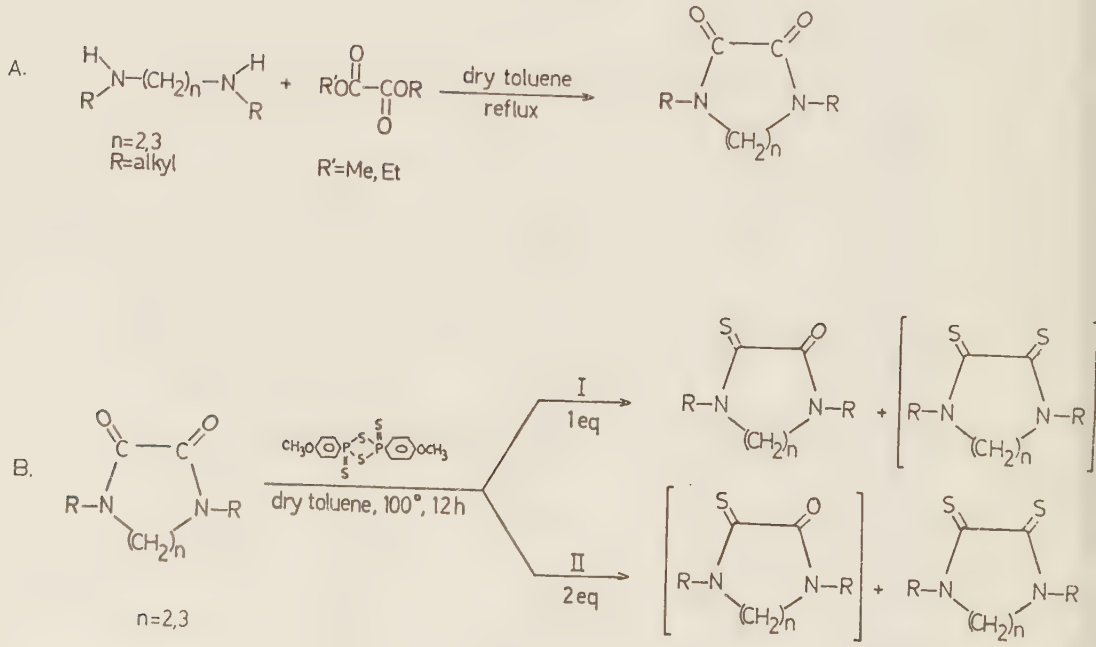
III

III	R	X	Y	Y'
a	H	CH_2	O	O
b	Me	CH_2	O	O
c	Et	CH_2	O	O
d	i-Pr	CH_2	O	O
e	$PhCH_2$	CH_2	O	O
f	$PhCH_2$	$C(Me)_2$	O	O
g	i-Pr	$C(Me)_2$	O	O
h	$PhCH_2$	CH_2	O	S
i	i-Pr	CH_2	O	S
j	i-Pr	CH_2	S	S
k	$PhCH_2$	CH_2	S	S
l	$PhCH_2$	$C(Me)_2$	S	S
m	Me	CH_2	S	S

RESULTS AND DISCUSSION

The preparations of the six- and seven-membered ring compounds IIa, b, d, IIIb-f, and IIIh-m have been carried out according to the general scheme shown below (Scheme 1).

Thiooxamides have commonly been prepared by reacting oxamides with phosphorus pentasulfide. However, the use of this standard method has very often been connected with isolation problems and the degree of thionation is difficult to control. Recently, a new thionation reagent, p-methoxyphenylthioxophosphine sulfide, was



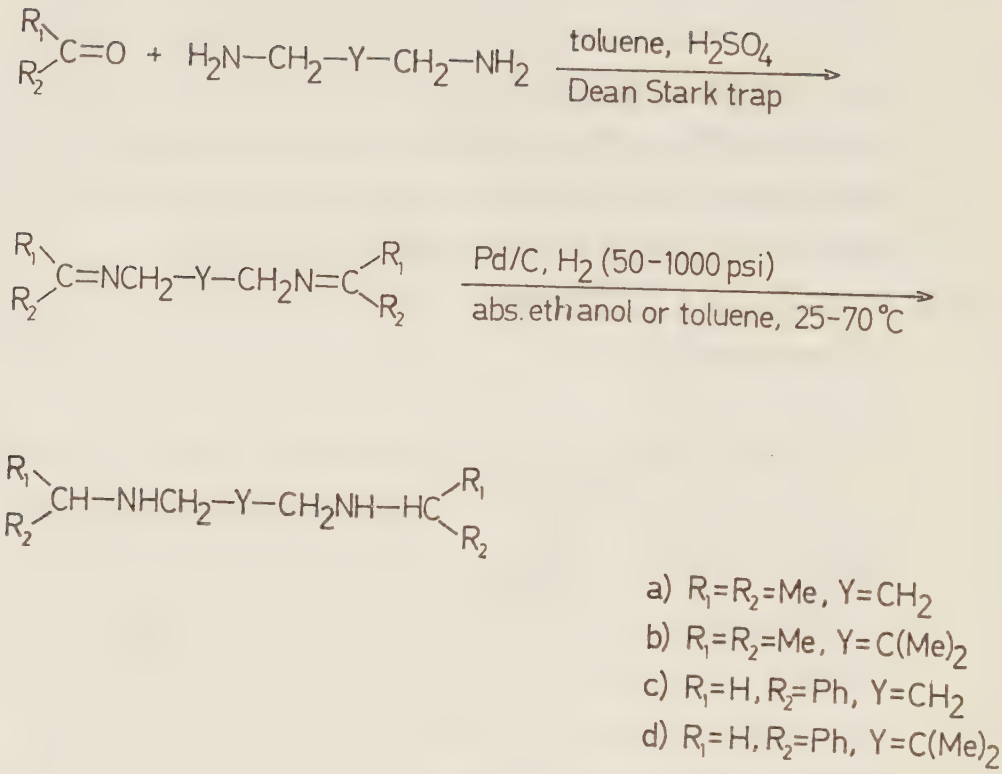
Scheme 1.

reported.[7] This reagent has so far not been used for the preparation of thiooxamides. As described below this cheap and readily available reagent gave high yields (80-100 %) of either dithio or monothio compounds under mild conditions depending on the amount of reagent used. No decomposition products could be detected and the work-up was simple: column chromatography (silica gel) followed by re-crystallization. Analytically pure compounds were obtained by preparative thin layer chromatography.

Seven-membered rings

All N,N'-dialkyl-1,3-diaminopropanes used in the ring formation reactions (Scheme 1), except for the N,N'-diethyl[8] compound, were prepared according to Scheme 2.

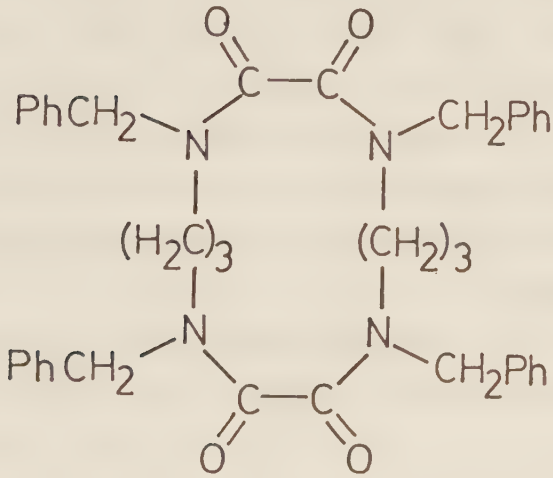
If primary amines and aldehydes were used as starting materials, the Schiff bases (imines) were obtained in almost quantitative yields. The secondary diamines were prepared by hydrogenation in a Parr apparatus using ethanol or toluene as solvent under moderate hydrogen pressure (about 50 psi). The catalyst used in all reactions was palladium on carbon (10 %). The condensation reaction between acetone and primary amines was slow and only small amounts of the Schiff base were formed under the above mentioned conditions. However, if the primary amine was dissolved in an excess of acetone and the hydrogenation was carried out under elevated hydrogen pressure (about 1000 psi) a high yield (95-100 %) of the desired secondary amine was obtained. A small quantity of 2-propanol could also be isolated.



a) $R_1=R_2=Me$, $Y=CH_2$
b) $R_1=R_2=Me$, $Y=C(Me)_2$
c) $R_1=H$, $R_2=Ph$, $Y=CH_2$
d) $R_1=H$, $R_2=Ph$, $Y=C(Me)_2$

Scheme 2.

Reacting diamines with methyl oxalate in dry benzene, toluene or xylene (Scheme 1) gave the cyclic compounds in moderate to high yields (20-75 %) depending on the N-substituents. To obtain these yields, the concentration of the starting materials must be less than 0.1 M. With higher concentration large amounts of open chain polymeric materials were formed. It was found that the best yields were obtained if toluene was used as solvent and dimethyl oxalate as reagent. Higher boiling solvents, e.g. xylene, caused thermal decomposition of the oxalate. We also found that the amount of open chain polymeric by-products increased when benzene was used as solvent. Attempts to prepare IIIe using oxalyl chloride instead of oxalate gave a cyclic dimer IV in 50 % yields together with open chain polymers. The desired monomeric product could not be detected.



IV

All attempts to prepare IIIg failed. Reaction times up to 90 h left the starting materials almost unchanged. Only traces of IIIg could be detected. The reason for this failure is probably that the isopropyl groups on nitrogen and the two geminal methyl groups on the carbon chain sterically interfere and prevent the attack of the oxalate.

Several attempts were made to prepare the N-unsubstituted compound (IIIa). In all cases, even when high dilution technique was used, only polymeric materials were formed. Attempts to cleave the N-benzyl bond in IIIe catalytically according to Usković et al.[9] also failed. Analyses showed that no reaction occurred in spite of long reaction times and high hydrogen pressure.

As mentioned above the monothio and dithio analogues of the oxamides were prepared using p-methoxyphenylthioxophosphine sulfide in absolute toluene at 100 ^{o}C (Scheme 1, B II). A slight excess (10 %) of the reagent and reaction times of about 12 h yielded almost pure dithio compounds in very high yields (95-100 %). Monothio compounds could also be isolated in high yields (80 %) if half the amount of the thionation reagent was used (see Scheme 1, B I). The thionation reaction has not been investigated in detail from the mechanistical point of view, but it is obviously a stepwise reaction, first the monothio compound is formed and then the dithio compound.

Prolonged storage of the reagent reduced its efficiency, probably because of decomposition reactions.

Six-membered rings

Preparation of piperazine-2,3-diones by reacting 1,2-diamines and oxalic esters in the absence of solvent has been reported.[10] These reactions were satisfactorily effected when the diamines contained one primary and one secondary amino group. If unsubstituted amines or symmetrically substituted amines were reacted with oxalic esters according to this method, only polymers were detected.

Moderate to high yields (< 60 %) of IIb were obtained by refluxing N,N'-dimethylethylenediamines and ethyl oxalate in dry benzene for 24 h. Only a small quantity of by-products was formed. Using high dilution technique, the N-unsubstituted compound IIa was prepared in moderate yield (ca 30 %). Ethyl oxalate and the diamine were added slowly (dropwise) to a large volume of boiling ethanol. Insoluble polymeric materials separated at once. Filtration and evaporation gave the desired compound together with some low molecular weight open chain polymers. Recrystallization afforded an analytically pure compound.

The dithio analogue (IId) was prepared from IIb in good yields (80-90 %) using the same thionation reagent as above. It was, however, not possible to prepare the dithio or monothio analogues of the N-unsubstituted compound. Analyses showed that polymerisation of the thionated product occurred. Neither starting materials nor the desired compound could be detected by mass spectroscopy. No further studies of the nature of the bad smelling products were carried out.

Five-membered rings

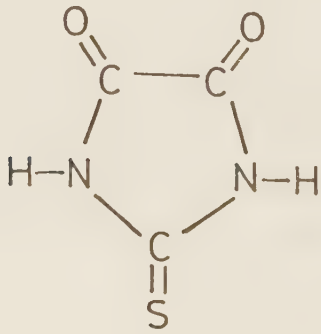
The five-membered rings (Ia, b) could not be prepared by the methods mentioned above. The N,N'-disubstituted compound (Ib) was isolated in an anodic bis-acetoxylation (large scale laboratory electrolysis)[11] of N,N,N',N'-tetramethyloxamide. A probable mechanism of the reaction is shown below (Scheme 3).

The desired product slowly separates from the distilled reaction mixture. Yields are low (< 10 %).

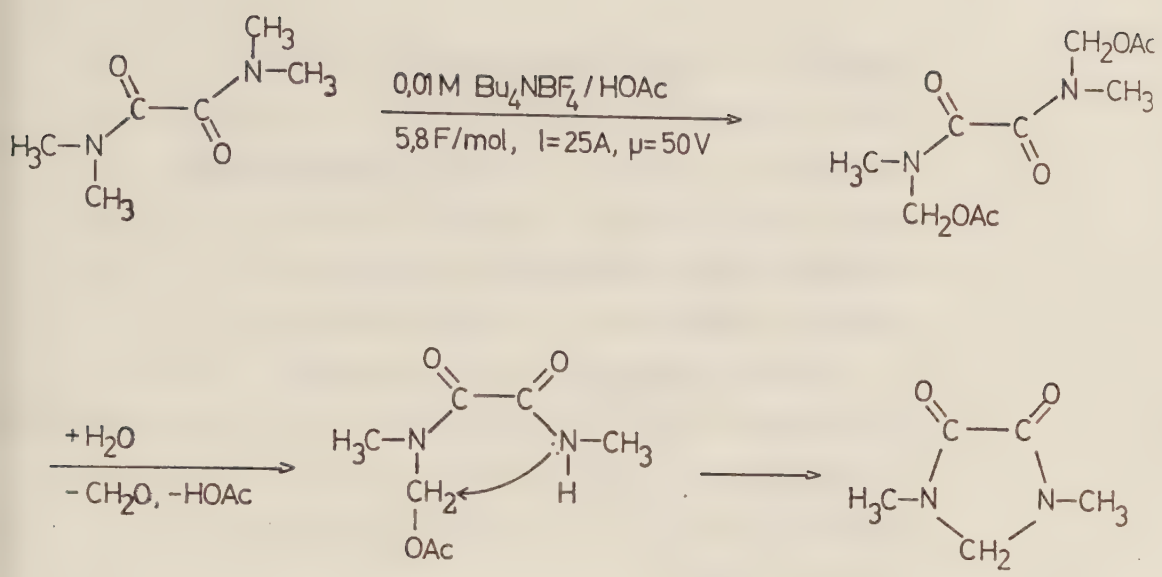
Many attempts were made to prepare the N,N'-unsubstituted compound (Ia). All attempts were, however, unsuccessful. Some of these experiments are discussed below.

To a mixture of oxamide and sodium hydride in THF was added during a long period of time paraformaldehyde dissolved in DMF (Scheme 4). Analyses of the reaction mixture showed that the main part of the starting materials remained unchanged, and the presence of a small amount of polymers. When methylene diamine hydrochloride was reacted with oxalic esters in the presence of triethylamine to keep the methylene diamine concentration low, the only products formed were oxamide and polymers (Scheme 4B).

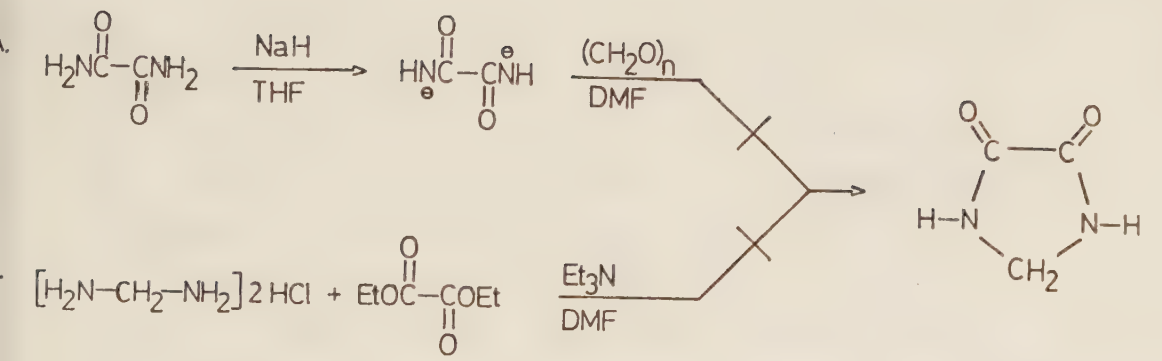
Catalytic hydrogenation of thioparabanic acid V in absolute



V



Scheme 3.

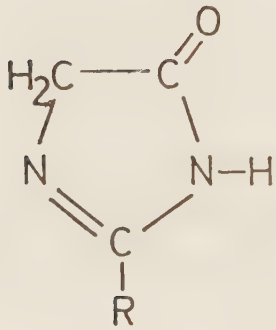


Scheme 4.

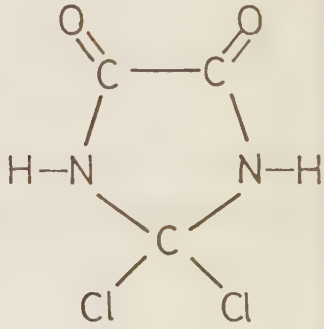
ethanol was also carried out. The analyses (mass spectrum) showed that a small amount of the desired compound Ia had been formed. It was, however, not possible to isolate the compound. After recrystallization the expected molecular ion peak, corresponding to the desired product, disappeared. Rearrangement to an open chain compound or decomposition had probably occurred.

A similar observation[12] was made in attempts to isolate 4(5)-imidazolone (VIa), a compound related to Ia. This was interpreted in terms of an equilibrium with an open chain form. The substituted compound VIb and the dichloro compound VII could, however, be isolated in high yield.

a) R=H
b) R=Me



VI



VII

EXPERIMENTAL SECTION

Preparation of diamines

N,N'-Dimethyl-1,2-diaminoethane, N,N'-dimethyl-1,3-diaminopropane and 2,2-dimethyl-1,3-diaminopropane were commercial products.

N,N'-Dibenzyl-1,3-diaminopropane and N,N'-diisopropyl-1,3-diaminopropane were prepared according to Sandström and Sjöstrand.[13]

N,N'-Diisopropyl-2,2-dimethyl-1,3-diaminopropane. 2,2-Dimethyl--1,3-diaminopropane (102 g, 1.0 mol), acetone (168 g, 3.0 mol) and abs. ethanol (50 ml) were mixed in an autoclave to which was added 1.0 g 10 % Pd/C catalyst. Hydrogenation at 1000 psi, removal of the catalyst and distillation gave the desired product (175 g, 95 %) b.p. 76-78 ^{o}C/12 mm.

N,N'-Dibenzyl-2,2-dimethyl-1,3-diaminopropane. A mixture of 2,2-dimethyl-1,3-diaminopropane (51 g, 0.5 mol), benzaldehyde (106 g, 1.0 mol) and toluene (200 ml) was refluxed until the theoretical amount of water had separated (Dean stark trap). The reaction mixture was allowed to cool and was then transferred to a Parr bottle to which was added 1.0 g 10 % Pd/C catalyst. Hydrogenation at 50 psi, removal of the catalyst and distillation afforded the product (135 g, 95 %), b.p. 130-132 ^{o}C/0.4 mm.

These amines gave ^{1}H NMR spectra in agreement with the expected structure. They are otherwise regarded as characterized by the derivatization to oxamides, and mono- and di-thiooxamides.

Preparation of the cyclic compounds I-III

Experimental data are given in the Table.

N,N'-Dimethylimidazolidine-2,3-dione (Ib). This compound crystallized from the distilled reaction mixture from the bis-acetoxylation of N,N,N',N'-tetramethyloxamide.[11] (The main product of the reaction is the bisacetate.)

Piperazine-2,3-dione (IIa). Diethyl oxalate (14.6 g, 0.1 mol) in 200 ml abs. ethanol and ethylene diamine (6.0 g, 0.1 mol) dissolved in 200 ml abs. ethanol and placed in separate dropping--funnels were simultaneously added dropwise very slowly (several hours) to boiling abs. ethanol (1.0 l). The reaction mixture was refluxed for another 12 h and then filtered as warm as possible and, after cooling, evaporated to dryness. Recrystallization of the residue from water gave the desired product as colourless prisms.

N,N'-Dimethylpiperazine-2,3-dione (IIb). Diethyl oxalate (14.6 g, 0.1 mol) and N,N'-dimethyl-1,2-diaminoethane (8.8 g, 0.1 mol) were refluxed for 24 h in dry benzene (500 ml). On cooling, a crystalline product separated. Recrystallization from toluene gave an analytically pure compound.

N,N'-Dimethylpiperazine-2,3-dithione (IId). A mixture of IIb (0.71 g, 0.005 mol) and p-methoxyphenylthioxophosphine sulfide[7] (2.2 g, 0.0055 mol) in dry toluene (10 ml) at 100 ^{o}C was stirred for 12 h. After cooling, the reaction mixture was poured on a column containing silica gel. The desired product was eluted with chloroform. After evaporation the residue was recrystallized from ethanol. Dark red needles were obtained. Yield 0.75 g (80 %), m.p. 228-230 ^{o}C.

N,N'-Dialkyl-perhydrodiazepine-2,3-diones (IIIb-f). – General method of preparation. A mixture of N,N'-dialkyl-1,3-diaminopropane (0.01 mol) and dimethyl oxalate (0.01 mol) in dry toluene (150-200 ml) was refluxed for 70 h. Evaporation and recrystallization yielded the products in moderate to high yields.

General method of preparation of the mono and dithio analogues (IIIh-m) of the N,N'-dialkyl-perhydrodiazepine-2,3-diones. The same method as for IId was used in the preparation of the dithio compounds. The amount of p-methoxyphenylthioxophosphine sulfide (the thionation reagent) was reduced to 50 % in preparation of the monothio compounds. Preparative thin layer chromatography gave analytically pure compounds on elution with chloroform.

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Table. Experimental data for compounds I-III.

Compd.	M.p./°C	Analysis (%)	Calc.	Found	Recryst. Solvent	NMR[a]	Yield[e] (%)
Ib	246-247	$C_5H_8N_2O_2$	C 46.87 H 6.29 N 21.86	C 46.80 H 6.29 N 22.00	—	3.08 (s6), 4.70 (s2)	< 10
IIa	279-280	$C_4H_6N_2O_2$	C 42.11 H 5.30 N 24.55	C 41.7 H 5.36 N 24.10	Water	3.25 (s2), 3.54 (s4)[f]	30
IIb	176-179	$C_6H_{10}N_2O_2$	C 50.70 H 7.09 N 19.70 O 22.40	C 50.50 H 7.15 N 19.60 O 22.40	Toluene	3.15 (s6), 3.65 (s4)	40
IId	228-230	$C_6H_{10}N_2S_2$	C 41.4 H 5.78 N 16.1 S 36.8	C 41.4 H 5.83 N 16.0 S 36.9	Ethanol	2.8 (s6), 3.6 (s4)	80
IIIb	191-193	$C_7H_{12}N_2O_2$	C 53.83 H 7.74 N 17.94 O 20.49	C 53.60 H 7.73 N 17.90 O 20.77	Ethanol	2.05 (m2), 3.10 (s6), 3.45 (m4)	55
IIIc	83-84	$C_9H_{16}N_2O_2$	C 58.67 H 8.75 N 15.20 O 17.36	C 58.70 H 8.86 N 15.40 O 17.60	Ethanol/ ether 2:1	1.15 (t6), 1.98 (m2), 3.50 (m8)	35-40

IIId	220-221	$C_{11}H_{20}N_2O_2$	C 62.23 H 9.49 N 13.20 O 15.07	C 62.20 H 9.36 N 13.20 O 15.30	Ethanol/ ether 2:1	1.14 (d12), 1.83 (m2), 3.29 (m4), 4.77 (m2)[b]	20-30
IIIe	154-155	$C_{19}H_{20}N_2O_2$	C 74.00 H 6.54 N 9.08 O 10.38	C 73.70 H 6.57 N 9.00 O 10.73	Ethanol	1.29 (m2), 3.26 (m4), 4.59 (s4), 7.27 (s10)	60
IIIf	252-253	$C_{21}H_{24}N_2O_2$	C 74.97 H 7.19 N 8.32 O 9.52	C 74.80 H 7.37 N 8.31 O 9.52	Ethanol	0.80 (s6), 3.01 (s4), 4.72 (s4), 7.27 (s10)	50-55
IIIh	131-133	$C_{19}H_{20}OS$	C 70.33 H 6.21 N 8.63 S 9.88	C 69.25 H 6.21 N 8.42 N 9.70	Ethanol	1.29 (m2), 3.13 (m2), 3.40 (m2), 4.60 (m2), 5.20 (m2)	80
IIIi	191-192	$C_{11}H_{20}N_2OS$	C 57.86 H 8.83 N 12.27 S 14.04	C 57.60 H 8.86 N 12.10 S 14.10	Ethanol	1.13 (m12), 1.92 (m2), 3.26 (m2), 3.55 (m2), 4.82 (m1), 5.67 (m1)	80
IIIj	119-120	$C_{11}H_{20}N_2S_2$	C 54.05 H 8.25 N 11.46 S 26.24	C 54.10 H 8.28 N 11.50 S 26.00	Ethanol	0.86 (m12), 1.55 (m2), 3.17 (m4), 5.67 (m2)[c]	90-95

IIIk	110-111	$C_{19}H_{20}N_2S_2$	C 67.02	C 66.90	Ethanol	1.08 (m2),	90-95
			H 5.92	H 5.88		3.12 (m4),	
			N 8.23	N 8.06		4.98 (q4)[d]	
			S 18.83	S 18.65			
IIIl	233-234	$C_{21}H_{24}N_2S_2$	C 68.43	C 68.60	Ethanol	0.58 (s6),	90-95
			H 6.56	H 6.50		3.10 (q4),	
			N 7.60	N 7.61		5.20 (q4)[c]	
			S 17.39	S 16.20			
IIIm	189-190	$C_7H_{12}N_2S_2$	C 44.65	C 44.30	Toluene	2.20 (m2),	80-85
			H 6.42	H 6.58		3.44 (s6),	
			S 34.05	S 34.25		3.58 (m4)[b]	

[a] In $CDCl_3$ unless otherwise stated, δ in ppm from TMS.

[b] In $CHCl_2F$.

[c] Isoquinoline at +100 ^{o}C with hexamethyldisiloxane as reference.

[d] o-Dichlorobenzene.

[e] Based on several experiments.

[f] In D_2O.

PAPER II

CONFORMATIONS AND BARRIERS TO INVERSION OF SEVEN-MEMBERED CYCLIC OXAMIDES AND THEIR MONOTHIO AND DITHIO ANALOGUES: A STUDY BY DYNAMIC NMR SPECTROSCOPY AND MOLECULAR MECHANICS.

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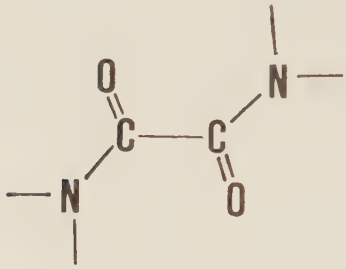
Abstract

Conformations and barriers to inversion of N,N'-dialkylperhydrodiazepine-2,3-dione and its monothio and dithio analogues have been studied by ^{1}H NMR spectroscopy and by molecular mechanics calculations. Experiments as well as calculations indicate that the compounds studied adopt a twist-boat conformation (C_2 symmetry). The inversion of the ring system involves a passage through a C_s structure with a planar s-cis (thio)oxamide unit. The free energy barriers increase in the order oxamide < monothiooxamide < dithiooxamide.

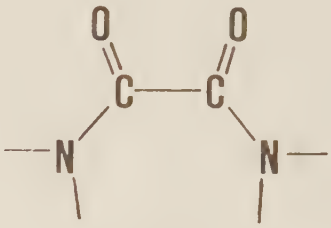
The calculations indicate that the dominant part of the barrier is of steric origin, the electrostatic contribution is less than 20 % of the total barrier height.

Introduction

Oxamide and N-alkyl substituted oxamides adopt a planar s-trans conformation provided that the conformation of the N-substituted amide unit is Z[1-5]. If at least one of the amide units has an E conformation, repulsive steric interactions in the planar s-trans



s-trans



s-cis

conformation between the N-substituent in one half of the molecule and the carbonyl group in the other are relieved by rotation around the central carbon-carbon bond. Thus, N,N'-dimethyloxamide with both N-methyl substituted amide units in the Z conformation is planar s-trans[3], while N,N,N',N'-tetramethyloxamide is twisted by 71.4° according to X-ray diffraction studies[2]. Replacement of one or both oxygens with sulphur increases the twist, N,N,N',N'-tetramethylmonothiooxamide and N,N-dimethyl dithiooxamide are 87.4° and 93.1° twisted, respectively, reflecting the relative steric size of oxygen and sulphur[2]

The planar s-cis conformation of oxamides and their monothio and dithio analogues may be expected to be disfavoured due to strong steric repulsions between the E substituents on nitrogen and to repulsive electrostatic interactions between the two (thio)carbonyl

groups. To our knowledge, no observations of the s-cis conformation in acyclic oxamide derivatives have been reported.

The twisted conformation of tetraalkyl substituted oxamides and their thio derivatives makes it possible to study the barrier to rotation through a planar transition state by the DNMR technique and thus obtain a quantitative estimate of the relative steric and electrostatic effects of oxygen and sulphur. Carter and Sandström[6] studied the barrier to rotation around the central carbon-carbon bond in tetrabenzyloxamide and its monothio and dithio analogues. They found the rotational barrier ($\Delta G^{\ddagger}$) to be very sensitive to replacement of oxygen with sulphur, the free energy barriers increasing in the order oxamide (9.7 kcal/mol) monothiooxamide (17.6 kcal/mol), and dithiooxamide (> 24 kcal/mol). The barriers were interpreted in terms of steric interactions in a planar s-trans transition state between the oxygen or sulphur atom in one half of the molecule and the benzylic methylene group in the other half. This interpretation was supported by empirical calculations of steric interactions.

Twisted oxamides are chiral molecules and recently Mannschreck and co-workers separated the enantiomers of N,N,N',N'-tetramethyl dithiooxamide[7]. They found the barrier to racemization for this molecule to be 25.6 kcal/mol ($\Delta G^{\ddagger}_{334}$).

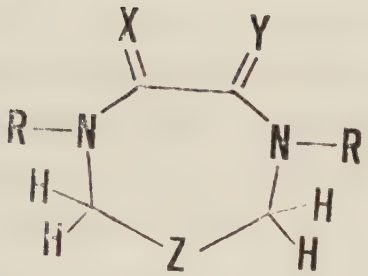
The rotational barriers for oxamides obtained so far provide an estimate of steric interactions in a planar s-trans conformation. The purpose of the present work is to investigate the corresponding barrier to passage through a planar s-cis conformation in order to obtain an estimate of the electrostatic and steric interactions in

this conformation.

We have investigated a series of seven-membered cyclic oxamides and their monothio and dithio analogues by studying their temperature dependent ^{1}H NMR spectra. In cyclic oxamides of appropriate ring size the oxamide unit is forced to adopt a twisted s-cis conformation, and the inversion of the ring system should involve the passage of the carbonyl or thiocarbonyl groups in a planar or close to planar s-cis conformation.

The seven-membered ring system was chosen since models indicate that it is large enough to keep the geometry of the oxamide unit largely unperturbed in the preferred ring conformation, but still small enough to only have a limited number of possible conformations, thus facilitating the interpretation of the NMR spectra. The experimental results will be compared to those obtained for the corresponding acyclic compounds. To aid in the interpretation of the NMR spectra and the observed inversion barriers, minimum energy conformations and conformational energies were calculated by the molecular mechanics method. Calculations on six-membered cyclic oxamides indicate that the inversion barriers in such compounds are too low to make a DNMR study feasible.

The compounds studied in this work are shown below.



Compound	R	X	Y	Z
I	$CH(CH_3)_2$	O	O	CH_2
II	$PhCH_2$	O	O	CH_2
III	$PhCh_2$	O	O	$C(CH_3)_2$
IV	$CH(CH_3)_2$	O	S	CH_2
V	$PhCH_2$	O	S	CH_2
VI	$CH(CH_3)_2$	S	S	CH_2
VII	$PhCH_2$	S	S	CH_2
VIII	$PhCH_2$	S	S	$C(CH_3)_2$

Experimental and computational section

Materials. The preparation of the compounds studied in this work has been described previously[8].

NMR measurements. All spectra were recorded on a JEOL Model JNM-MH-100 NMR spectrometer, equipped with a standard variable tempe-

rature attachment (VT 3-C). The samples were 0.4-0.5 M solutions in $CHCl_2F$ or $CDCl_3$ for low and isoquinoline for high temperature measurements. Tetramethylsilane (TMS) or hexamethyl disiloxane (HMSO) was added to the solvents to provide the internal lock signal. The temperatures were measured as described elsewhere[9].

The rate constants were evaluated by visual fitting of experimental to calculated spectra. The theoretical spectra of the isopropyl methyls were obtained by superposition of two spectra for uncoupled two-site cases using the McConnell equation for the two-site exchange[10]. The effect of coupling was taking into account by suitable amplitude factors. The determination of the effective transverse relaxation time (T_2) was performed as described in Ref.11.

For one of the compounds (I) a total bandshape analysis was performed. For the remaining compounds rate constants and free energies of activation were determined at 4-5 different temperatures around the coalescense temperature.

Molecular mechanics calculation. These were performed using the MM1 program developed by Allinger and co-workers, employing their 1973 force-field for the hydrocarbon parts of the molecules[12]. The (thio)oxamide unit was treated as a composite of two (thio)amide units, using the parameter set for amides and thioamides previously employed in calculations on conformational energies and rotational barriers for this class of compounds[9,13,14]. The remaining parameters necessary for the calculations, mainly parameters for the connection of the two (thio)amide units, were estimated for the

purpose of this investigation, with guidance from the corresponding values in a force-field for α-diketones[15]. Good experimental energy and geometry data for (thio)oxamides are at present too scarce to make a complete optimization of the (thio)oxamide force-field meaningful. Furthermore, for more general calculations on this class of molecules the π-electron energy should be explicitly taken into account. The force-field parameters used for the (thio)oxamide units are given in Table 1.

Electrostatic interactions were calculated by two methods using (i) the dipole interacion model, employing point dipoles placed at the midpoints of the bonds[16] and (ii) the charge interaction model with atomic charges obtained from CNDO/2 calculations on tetramethyloxamide and its dithio analogue[17]. Bond moments and fractional atomic charges are given in Table 1. In all calculations of the electrostatic interactions an effective dielectric constant of unity was employed.

The energies of the molecules were minimized with respect to all degrees of freedom using the dipole interaction model to calculate the electrostatic interactions. Symmetry constraints were included where applicable. Charge interaction energies were dealt with separately and added to the results of the energy minimizations with the dipole interaction energies subtracted out.

Results

At ambient temperature the ^{1}H NMR spectra of the cyclic oxamides I-III show a doublet for the isopropyl methyls in I and a sharp singlet for the benzylic methylene protons in II and III. The signals broaden at lower temperatures and split at about 209 K into two isopropyl methyl doublets of equal intensities in the spectrum of I, and at 213 and 248 K into an AB pattern for the benzylic protons in II and III, respectively. In III the ring methylene protons show up as a singlet at probe temperature and as an AB quartet at low temperatures (< 238 K). The signal from the geminal methyl groups in III is a sharp singlet at all temperatures investigated (down to 210 K). The AB shift for the benzylic protons in III, 152.7 Hz, is much larger than the corresponding shift in II, 33.2 Hz, indicating different conformational preferences of the benzyl groups in II and III.

The ambient temperature spectra of the dithiooxamides VI-VIII display two doublets (1:1) for the isopropyl methyls in VI and AB patterns for the benzylic methylene protons in VII and VIII and for the ring methylene group in VIII. All signals broaden at higher temperatures and above 435 K they coalesce into one doublet for the isopropyl methyls in VI and above 448 K into singlets for the methylene groups in VII and VIII. The coalescence for the benzylic methylene signals in VIII lies above the upper temperature limit of the spectrometer (473 K). In VIII as in III the singlet due to the geminal ring methyl groups does not change with temperature. The relative size of the AB shifts in VII and VIII show the same pattern as

in II and III. In VII the benzylic AB shift is 20.6 Hz, while in VIII the corresponding shift is 194.6 Hz. The temperature dependence of the ^{1}H NMR spectra of the oxamides and of the analogous dithio oxamides is thus very similar, but the temperature interval in which the spectral changes occur is displaced by more than 200 degrees to higher temperatures on going from oxamides to dithiooxamides. Due to lower molecular symmetry, the spectra of the monothiooxamides IV and V are more complex than those of the corresponding (dithio)oxamides. Four somewhat overlapped doublets of equal intensities for the isopropyl methyls in IV are observed at low temperatures. These signals coalesce at 299 K into two doublets. The downfield one is assigned to the thioamide half of the molecule from a comparison with the corresponding signals in the spectra of I and VI. In V the benzylic protons give rise to two well-separated AB spectra below probe temperature. The downfield one is assigned to the thioamide unit. The AB shifts in the spectra of this compound are significantly temperature dependent. At 254 K the shifts are 33.4 and 26.8 Hz, respectively, at 300 K they have decreased to 26.8 and 16.3 Hz, respectively. The two AB quartets coalesce into two singlets at about 305 K.

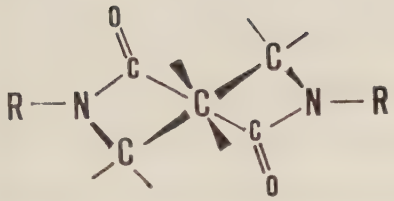
Chemical shifts and coupling constants for compounds I-VIII are given in Tables 2 and 3. Rate constants were evaluated from the temperature-dependent bandshapes as described in the Experimental part. The corresponding free energy barriers are given in Table 4.

For III and VIII two different proton groups, the benzylic methy-

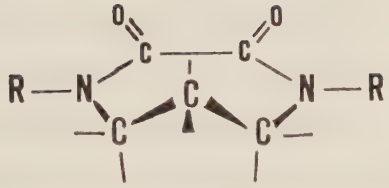
lene protons and the ring methylene protons, could be studied. The two sets of rate constants thus obtained were identical within error limits at all temperatures where a comparison could be made, indicating that they correspond to the same dynamic process.

Discussion

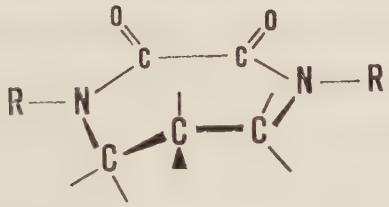
Conformations of I-VIII. From the ^{1}H NMR spectra described above it can be concluded that the four isopropyl methyls in I and VI, and the four benzylic methylene protons in II, III, VII and VIII are pairwise equivalent or enantiotopic in the lowest energy conformation of the molecules. This is only consistent with conformations having a C_2 axis (possibly pseudorotationally averaged) or a mirror plane through the ring system and bisecting the (thio)carbonyl - (thio)-carbonyl bond. The conformational freedom of the cyclic oxamides is restricted by the rigidity of the (thio)amide units, and thus only conformations with planar or close to planar (thio)amide units may be considered as candidates for the low energy conformations. This restriction makes the ring system in the compounds studied in this work similar to the 1,3-cycloheptadiene ring system, for which calculations indicate that the molecule has three low energy conformations with C_2 (twist-boat), C_s or C_1 symmetry[18]. The three conformations have essentially identical energies and are separated by very small energy barriers. The corresponding conformations applied to cyclic oxamides are shown below.



C_2



C_s



C_1

Other formally possible conformations like twist-chair, chair and boat all require considerable twisting around the amide C-N bond(s) and may therefore be excluded.

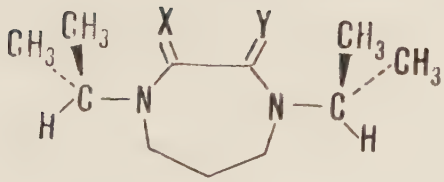
Unfortunately, the ring methylene resonances in I, II and IV-VII are not sufficiently resolved at low temperatures to allow an unambiguous analysis of this part of the spectra and to deduce the preferred conformation from these spectral data. However, the spectra of III and VIII, showing a sharp singlet for the geminal methyl groups attached to the ring at all temperatures investigated, are

only consistent with the C_2 (twist-boat) conformation. Strictly, these experimental data only allow the C_s and the C_1 conformations to be excluded for III and VIII, but molecular mechanics calculations clearly indicate that the C_2 conformation is very strongly preferred for all compounds studied in this work. The energy for the C_s conformation is calculated to be 9-20 kcal/mol higher than that for the C_2 twist-boat. The C_1 conformer lies ca 2 kcal/mol below the C_s conformer but still 7-18 kcal/mol above the C_2 twist-boat. More important, unrestricted energy minimizations show that the C_s and C_1 conformers are not local minima on the potential energy surface for the cyclic oxamides. As will be discussed below, the C_s conformation may in fact be regarded as a good model for the transition state geometry for the degenerate inversion process C_2 twist-boat $\rightleftharpoons$ C_2 twist-boat.

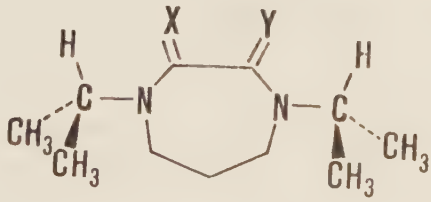
The X = C - C = Y (X=O,S; Y=O,S) dihedral angle for compounds I-VIII is calculated to be 61-65°, with the higher values for the sulphur compounds, showing in comparison with acyclic analogues (see Introduction) that the seven-membered ring system prohibits the relative steric size of oxygen and sulphur to be reflected in twisting around the central carbon-carbon bond. The calculated dihedral angles are close to the value found in an X-ray study for the twisting around the N-N bond in seven-membered cyclic azines (66.8^{o}) which also adopt a C_2 twist boat conformation[19].

N-alkyl conformations. As shown in Table 2 the resonances for the isopropyl methine protons appear at 4.77 ppm for I, at 4.82 ppm

and 5.67 ppm for IV, and at 5.67 ppm for VI. The resonance position of the methine protons in N- (Z)-isopropyl groups in amides and thioamides has been shown to be very sensitive to the conformation of the isopropyl group. For amides the Z-isopropyl group conformation in which the methine proton is in or close to the amide plane and pointing towards the carbonyl group exhibits a methine proton resonance at 4.8-5.0 ppm, which is significantly downfield to the resonances for methine protons in other positions. For thioamides the corresponding value is 5.5-6.3 ppm[9]. The methine proton resonances in I, IV and VI thus indicate that this proton eclipses (or nearly so) the amide C-N bond in the preferred conformation (conformer B). This preference is apparently quite strong, since the observed shifts are close to the shifts found for the corresponding "frozen" N-isopropyl conformer in amides and thioamides. Molecular mechanics calculations of the relative energies of conformations A and B support this conclusion. Conformer B is calculated to be lower in energy by 0.32, 0.80 and 1.43 kcal/mol for I, IV and VI, respectively.



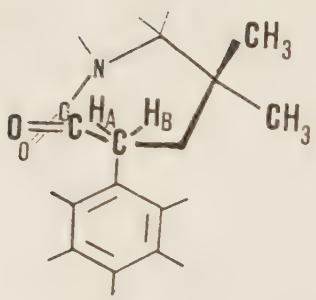
A



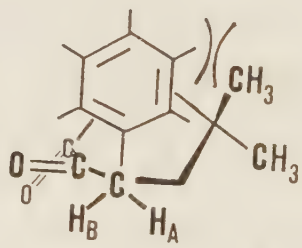
B

The conformation of the benzyl groups in II, III, V, VII and VIII may also be inferred from the chemical shift data for these compounds. As mentioned above, $\Delta\nu_{AB}$ is much larger for III and VIII, with geminal methyl groups attached to the ring, than for II and VII. The large $\Delta\nu_{AB}$ in III and VIII indicates that one of the benzylic methylene protons is pointing towards the (thio)carbonyl group. The size of the observed $\Delta\nu_{AB}$ is similar to those found for the Z-methylene protons in amides and thioamides substituted on nitrogen with primary alkyl groups which have been found to adopt an antiparallel perpendicular arrangement[13].

In the N-benzyl compounds studied in this work, the benzyl groups may have two nonequivalent approximately perpendicular conformations, C and D (see below). Fast interchange (on the NMR time-scale) between these conformations tends to reduce the $\Delta\nu_{AB}$.



C



D

However, in III and VIII the geminal methyl groups may interfere with the phenyl group in conformation D, leaving this conformation essentially unpopulated with a large (unaveraged) AB shift as the result.

This interpretation is supported by molecular mechanics calculations, which indicate that for II and VII two stable conformers corresponding to C and D are present, while for III and VIII no local minimum corresponding to conformation D is obtained. The X=C-N-C-C(phenyl) dihedral angles are calculated to be less than 90°, varying between 62 and 66°, but the potential surface around the minimum is very shallow.

Barriers to inversion. The free energy barriers to inversion for compounds I-VIII increase in the order oxamide < monothiooxamide < dithiooxamide (Table 4). The N-isopropyl compounds have slightly higher barriers than those of the N-benzyl substituted ones, reflecting small differences in steric interactions between the N-substituent and the ring system. The barriers for compounds II, V and VII are quite similar to those found by Carter and Sandström for the related acyclic tetrabenzyloxamide (9.7 kcal/mol) its monothio (17.9 kcal/mol) and dithio (>24 kcal/mol) analogues[6]. Mannschreck et al.[7] found the rotational barrier for tetramethyldithiooxamide to be 25.6 kcal/mol, and the barrier for tetrabenzyldithiooxamide should be close to this value. The barriers for these acyclic compounds were interpreted as mainly reflecting differences in steric interactions in a planar s-trans transition state between sulphur and oxygen in one half of the molecule and the E methylene group in the other. Simple empirical calculations of steric strain not including minimization of energy with respect to geometry, indicated that the energies for the s-cis conformations are extraordinarily

high. The barriers to inversion in I-VIII should reflect steric and electrostatic interactions in a planar or close to planar s-cis conformation of the (thio)oxamide unit. The similarity of the barriers in the acyclic and the corresponding cyclic compounds is therefore quite unexpected.

In the acyclic as well as the cyclic series of oxamide derivatives, the influence on the barrier of the replacement of oxygen with sulphur is very significant. Comparing the free energy barriers for compounds II, V and VII, replacement of one oxygen with sulphur increase the barrier by 5.0 kcal/mol. Replacement of both oxygens in II with sulphur gives an increase by 12.6 kcal/mol. The corresponding barrier increases for tetrabenzyloxamide and its thio derivatives are even larger, 7.9 and >14.3 kcal/mol, respectively. If the barrier found for tetramethylditiooxamide is taken to represent the undetermined barrier for tetrabenzyldithiooxamide, the latter value becomes 15.9 kcal/mol. These comparisons show that the height of the barrier through a s-trans transition state is significantly more sensitive to the sulphur/oxygen exchange than is the barrier through a s-cis transition state.

In order to further analyse the data presented above, and to obtain an estimate of the relative importance of the steric and electrostatic contributions to the inversion barriers of I-VIII, conformational energies were calculated by the molecular mechanics method as described in the Experimental and Computational section. The C_s structure described above was used as a transition state model. It was shown to be a local maximum on the potential energy surface by calculating the

energy changes for small stepwise increases of the (thio)carbonyl - - (thio)carbonyl dihedral angle. A possible transition state alternative, having all ring carbon atoms in one plane, was calculated to be >20 kcal/mol higher in energy. Other formally possible transition state structures all involve large twists around the (thio)amide bond(s) with concomitant very high energies. Calculated inversion barriers using two methods for calculating the electrostatic interactions are summarized in Table 5.

The free energies of activation were determined at significantly different temperatures, spanning a large temperature interval (ca 200 deg.). In order to make quantitative comparisons with calculated values meaningful, activation enthalpies were evaluated from the free activation energies in Table 4 and the activation entropy found for I. The similarity of compounds I-VIII justifies this procedure. The activation enthalpies are given in Table 5.

The agreement between the experimental and calculated barriers is very satisfactory, considering the approximations involved in the calculations. It should be noted that the calculated values refer to isolated molecules in the gas phase. Consequently we do not wish to place too much emphasis on the agreement between the absolute heights of experimental and calculated values. However, the calculated numbers clearly provide a basis for the interpretation and analysis of the experimental data. As may be expected, the calculations using the charge interaction model to calculate the electrostatic interactions reproduce the experimental trends better than do the calculations employing the dipole approximation. In the following, we will therefore

mainly discuss the results from the former calculations.

The electrostatic contributions (charge interaction energies) to the calculated barriers are given in Table 5. These contributions constitute only a minor part (8-17%) of the total heights of the barriers. Steric interactions, notably angle bending in the (thio)oxamide unit and nonbonded van der Waals repulsions between the (thio)carbonyl groups, are predominant. The $C(sp^2)$-$C(sp^2)$-N bond angle increases by ca 13° and the O=C-N angle decreases by ca 9° on going from the initial state to the transition state.

The experimental and calculated influences on the inversion barriers of the replacement of oxygen with sulphur in the three series I-IV-VI, II-V-VII and III-VIII are summarized in Table 6. The numbers are given relative to the oxamide parent compound. The electrostatic parts of the relative barriers are also included in Table 6. The agreement between the experimental and calculated values is quite good, but the calculated influence of the oxygen/sulphur exchange on the barriers is somewhat underestimated. The steric component is clearly dominant and even if the entire difference between calculated and experimental values were taken to be due to deficiences in the electrostatic model, the steric contributions would still be the larger ones.

It may thus be concluded that the dominant part of the inversion barriers is of steric origin, as well as the larger part of the effects on the barriers of replacing one or both oxygens with sulphur. The steric contributions reflect the larger steric size of the sulphur atom compared to the oxygen.

Returning to the acyclic tetrabenzyloxamide and its thio analogues, the steric contribution to the increase of the rotational barrier on replacement of oxygen, assuming a planar s-trans transition state, was calculated. Electrostatic contributions should play a minor role in this case. Tetramethyloxamide and its thio derivatives were used as models in the calculations. The calculated values for replacement of one or two oxygens are 6.5 and 15.5 kcal/mol, respectively. The experimental values ($\Delta\Delta G^{\ddagger}$) are 7.9 and 15.9 kcal/mol, respectively. Steric interactions thus completely account for the sensitivity of the inversion barrier through a s-trans transition state to the exchange of oxygen by sulphur, supporting the conclusions drawn by Carter and Sandström[6]. Inspection of the details of the calculations suggests that the observed differences in the barrier increments due to the sulphur/oxygen exchange for the s-cis transitions state in I-VIII and the s-trans transition state in the acyclic tetraalkyloxamides and its thio analogues, are mainly due to different possibilities to relax steric strain in the two series of compounds. In the s-trans conformer. substitution of oxygen by the larger sulphur leads to larger nonbonded repulsive interactions with the E-methylene group in the opposite half of the molecule. These interactions may partly be relaxed by bending of the (thio)amide unit, but a mode of bending that decreases the nonbonded repulsions on one side of the molecule, increases it on the other side. In the (cyclic)

s-cis conformation, such bendings may be distributed among several degrees of freedom, thus increasing the efficiency of the relaxation.

The rotational barrier through a s-cis transition state in the tetraalkylsubtituted acyclic oxamides should be appreciably higher than those found for the corresponding cyclic compounds I-VIII. The very large nonbonded repulsions between the E methylene groups in the acyclic s-cis conformer should increase the barriers compared to those for the cyclic molecules, where only a part of these interactions is present. Furthermore, the dihedral angle between the (thio)carbonyl groups is less than optimal in the cyclic compounds, leading to a relative increase of the initial state energy.

On the basis of preliminary calculations on tetramethyloxamide and its monothio and dithio analogues, the rotational barriers through a s-cis transition state in these molecules may be estimated to be approximately 20, 25 and 30 kcal/mol, respectively. More accurate calculations must await further development of the force-field employed in this work. In the s-cis transition state of the acyclic oxamides considerable twisting of the (thio)amide C-N bonds occurs. Thus, in a force-field suitable for more general calculations, explicit consideration of changes in the π-electron energy is probably required.

The free energy barriers to inversion in the dithiooxamides VI-VIII are high enough to make a separation of the enantiomers possible at room temperature. If such a separation can be successfully performed this would provide an opportunity to study the

chiroptical properties of cisoid dithiooxamides. Work along this line is in progress.

Acknowledgements

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Table 1. Force field parameters.

Table 2. ^{1}H NMR data for compounds I-VIII at ambient temperature

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Table 1. Force field parameters.

van der Waal's constants

$E_v = -2.25\varepsilon(r^*/r)^6 + 8.28 \times 10^5 \varepsilon \exp(-r/0.0736r^*)$

Atom	$r^*/\mathring{A}$	ε/kcal mol^{-1}
N	1.700	0.039
O	1.650	0.046
S	2.000	0.184

Stretching constants

$E_s = 71.94\ k_s(l-l_o)^2[\ 1 + C_s(l-l_o)]$ $\quad C_s = -2.00$

Bond	$l_o/\mathring{A}$	k_s/mdyn $\mathring{A}^{-1}$
C = O	1.215	10.80
C = S	1.626	5.14
C(sp^2) - N	1.367	5.00
C(sp^3) - N	1.449	3.40
C(sp^2) - C(sp^2)	1.500	6.00
C(sp^2) - C(sp^2) (phenyl)	1.394	8.07

Bending constants

$E_b = 0.021914k_b(\theta-\theta_o)^2[1 + C_f(\theta-\theta_o)]$ $\quad C_f = -0.006$

Angle	θ_o/deg.	k_b/mdyn $\mathring{A}$ rad^{-2}
N - C = O	124.0	0.50
N - C = S	125.0	0.50
C(sp^2) - C = O	121.0	0.50
C(sp^2) - C = S	122.3	0.40
C(sp^2) - C(sp^2) - N	112.7	0.40
C(sp^2) - C(sp^3) - N	109.5	0.42

Table 1 (cont.).

$C(sp^3) - N - C(sp^2)$	121.0	0.70
$C(sp^3) - N - C(sp^3)$	115.0	0.50
H - C - N	109.5	0.42
$C(sp^3) - C(sp^3) - N$	109.5	0.42
Out-of-plane $N(sp^2)$	0.0	0.05
Out-of-plane C(CO,CS)	0.0	0.80

Stretch-bend constants

$E_{sb} = 2.51124\ k_{sb}(\theta-\theta_o)[(l_1-l_o) + (l_2-l_o)]$

Atoms		k_{sb}/mdyn rad^{-1}
X - F - Y	F = 1strow atom	0.120
X - F - H	F = 1strow atom	0.040
X - S - Y	S = 2ndrow atom	0.160

X,Y = F or S

Torsional constants

$E_t = V_1/2\ (1 + \cos\omega) + V_2/2\ (1 - \cos2\omega) + V_3/2\ (1 + \cos3\omega)$

Angle		V_2	V_3	/kcal mol^{-1}
$X - C(sp^2) - C(sp^2) - Y$	(X,Y = O,S,N)	1.5		
$X - C(sp^2) - N - C(sp^3)$	(X = S,$C(sp^2)$)	6.0		
O = C - N - C		4.0		
$X - C(sp^3) - C(sp^3) - N$	(X = H,$C(sp^3)$)		0.53	
$X - C(sp^3) - N - Y$	(X = C,H Y = C)		1.0	
$C(sp^2) - C(sp^2) - C(sp^3) - N$			0.0	
X - C - C - Y	(Phenyl,X = C,H)	10.017		

Table 1 (cont.).

Bond moments

Bond	μ/D
C = O	2.91
C = S	3.23
C_{sp^2} - N	-1.16

Fractional atomic charges

Unit	C_{sp^2}	O/S	N	(N) - C_{sp^2}
Amide	+0.29	-0.32	-0.15	+0.09[a]
Thioamide	+0.15	-0.37	-0.03	+0.125[a]

a) averaged net charges of the methyl groups in tetramethyloxamide and tetramethyldithiooxamide.

Table 2. ^{1}H NMR data for compounds I-VIII at ambient temperature.

Compound	Solvent	δ^{a} (multiplicity^{b}, number of protons)
I	$CHCl_2F$	1.14(d 12), 1.83(m 2), 3.29(m 4), 4.77(m 2)
II	$CDCl_3$	1.29(m 2), 3.26(m 4), 4.59(s 4), 7.27(s 10)
III	$CDCl_3$	0.80(s 6), 3.01(s 4), 4.72(s 4), 7.27(s 10)
IV	$CDCl_3$	1.13(m 12), 1.92(m 2), 3.26(m 2), 3.55(m 2), 4.82(m 1), 5.67(m 1)
V	$CDCl_3$	1.29(m 2), 3.13(m 2), 3.40(m 2), 4.60(m 2), 5.20(m 2)
VI	isoquinoline[c)]	0.86(m 12), 1.55(m 2), 3.17(m 4), 5.67(m 2)
VII	o-dichlorobenzene	1.08(m 2), 3.12(m 4), 4.98(q 4)
VIII	isoquinoline[c)]	0.58(s 6), 3.10(q 4), 5.20(q 4)

a) ppm from TMS unless otherwise stated.

b) s = singlet, d = doublet, m = multiplet.

c) At 373 K with HMSO as reference.

Table 3. NMR data at slow exchange.

Compound	Signals studied	Solvent	Temp (K)	$\Delta\nu$(Hz)	J_{CH_3-CH}(Hz)	J_{AB}(Hz)
I	$CH(\underline{CH_3})_2$	$CHCl_2F$	204.2	5.9	6.8 6.8	- -
II	$Ph-\underline{CH_2}-$	$CDCl_3$	198.9	33.2		13.7
III	$Ph-\underline{CH_2}-$	$CDCl_3$	215.1	152.7		15.0
	$-C(CH_3)_2-\underline{CH_2}-$			39.5		15.5
IV	$CH(\underline{CH_3})_2$ [a]	$CDCl_3$	285.4	6.5	6.7 6.7	
	$CH(\underline{CH_3})_2$ [b]			7.5	7.1 7.1	
V	$Ph-\underline{CH_2}$ [a]	$CDCl_3$	253.5	33.4		14.3
	$Ph-\underline{CH_2}$ [b]			26.8		14.2
VI	$CH(\underline{CH_3})_2$	isoquinoline	429.2	7.2	6.7 6.7	

Table 3 (cont.).

VII	Ph-$\underline{CH_2}$	isoquinoline[c]	375.0	20.6	14.4
VIII	Ph-$\underline{CH_2}$	isoquinoline[c]	409.4	194.6	14.2
	-$C(CH_3)_2$-$\underline{CH_2}$-			41.9	14.4

a) amide unit

b) thioamide unit

c) HMSO as reference

Table 4. Free energy barriers to inversion for compounds I-VIII.

Compound	$\Delta G^{\ddagger}$ [a] (kcal/mol)	Temp (K)
I	11.1[b]	208.8
II	10.7	202.9
III	12.0	215.1
IV	17.2	298.6
V	15.7	284.4
VI	24.1	447.6
VII	23.3	431.5
VIII	23.2	409.4

a) estimated error $\pm$0.1 kcal/mol

b) $\Delta H^{\ddagger}$ = 10.0 $\pm$ 0.1 kcal/mol, $\Delta S^{\ddagger}$ = -5.2 $\pm$ 0.7 cal/mol.deg, only random errors calculated from the standard deviations in the Eyring plot are included

Table 5. Calculated inversion barriers and experimental $\Delta H^{\#}$ for compounds I-VIII.

Compound	Calc. barrier (kcal/mol)		Electrostatic part of the barrier (kcal/mol)	Exp. $\Delta H^{\ddagger}$ (kcal/mol)
I	DI[a]	13.7		10.0
	CH[b]	10.3	0.7	
II	DI	11.5		9.6
	CH	8.8	1.2	
III	DI	12.2		10.9
	CH	9.7	1.1	
IV	DI	15.7		15.6
	CH	13.4	1.1	
V	DI	13.6		14.2
	CH	12.2	1.9	
VI	DI	21.6		21.8
	CH	19.9	1.6	
VII	DI	19.2		21.1
	CH	19.4	3.3	
VIII	DI	19.6		21.1
	CH	18.9	2.3	

a) DI = dipole interaction model
b) CH = charge interaction model

Table 6. Calculated and experimental influences of replacement of oxygen with sulphur on the inversion barriers for I-VIII.

Compd.	$\Delta\Delta H^{\ddagger}$ exp. (kcal/mol)	$\Delta\Delta E$ calc. (kcal/mol)	Electrostatic part of $\Delta\Delta E$ (kcal/mol)
I	0	0	0
IV	5.6	3.1	0.4
VI	11.8	9.6	0.9
II	0	0	0
V	4.6	3.4	0.6
VII	11.5	10.6	2.0
III	0	0	0
VIII	10.2	9.2	1.2

PAPER III

Ab initio Calculations and Photoelectron Spectra of Cyclic Oxamides

By **Roland Isaksson** and **Tommy Liljefors**,* Department of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S–220 07 Lund, Sweden

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Ab initio Calculations and Photoelectron Spectra of Cyclic Oxamides

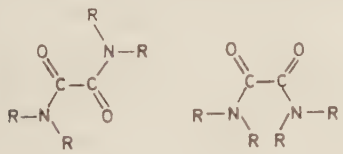
By **Roland Isaksson** and **Tommy Liljefors**,* Department of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden

Photoelectron spectra of five-, six-, and seven-membered cyclic oxamides in which the oxamide unit is forced to adopt an *s-cis* or twisted *s-cis* conformation have been recorded. The spectra have been interpreted using *ab initio* calculations. In comparisons with acyclic *s-trans* oxamides it is found that the influence of the *s-trans–s-cis* conformational change on the ionization energies is masked by the effects of the alkyl parts of the ring systems. Ionization energies of cyclic oxamides with different ring sizes show some effects due to twisting around the inter-carbonyl bond, but also in this case the alkyl parts of the ring systems strongly influence the spectra.

OXAMIDES and other α-dicarbonyl compounds have recently been intensively investigated by various spectroscopic methods. Photoelectron (p.e.) spectroscopy,[1-6] u.v. absorption and emission spectroscopy,[7,8] and n.m.r. spectroscopy[9] have been employed in studies on the electronic and steric interactions in this class of compounds.

Previous papers on p.e. spectra of oxamides have mainly been concerned with assignments of ionization events,[1] with the effects of *N*-alkylation on the ionization energies,[2,3] and with the energy separation of the n_+/n ionization processes.[4] Simple additivity rules for N-alkyl shifts have been established and have been very useful in the interpretation of p.e. spectra.[1,3]

For oxamide and its *N*-substituted derivatives, two planar conformations, *s-trans* and *s-cis*, are possible.



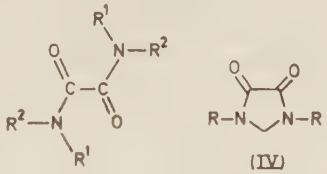
s-trans *s-cis*

Steric interactions may force the oxamide unit to adopt twisted conformations. Very little is known about the conformational properties of this class of compounds, but oxamide itself is *s-trans* and planar in the crystalline state.[10] *N*-Alkyl-substituted oxamides are generally also *s-trans*,[8] but may be more or less twisted around the carbonyl–carbonyl bond, depending on the degree of substitution. Tetra-alkyl-substituted oxamides are most severely twisted, with a dihedral angle close to 90°, according to n.m.r.[9,11,12] and dipole moment studies.[13] Strong dipole–dipole repulsions between the carbonyl groups and repulsive steric interactions between nitrogen substituents prevent the *s-cis* conformation from being significantly populated. The planar *s-cis* conformation may not even be a local minimum on the potential energy surface.[14]

All oxamide derivatives studied so far by p.e. spectroscopy have been *s-trans* or *s-transoid* (twisted *s-trans*). The only exception is a study by McGlynn *et al.* on imidazolidine-2,4,5-trione and some of its *N*-alkyl derivatives.[3] These compounds may be considered as *s-cis* oxamide derivatives, but the p.e. spectra were more conveniently interpreted in terms of a partition into urea and *s-cis* glyoxal.

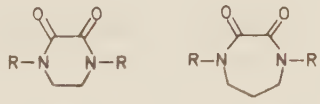
In this paper we report the p.e. spectra of some cyclic oxamides, in which the oxamide unit is forced to adopt an *s-cis*- or twisted *s-cis*-conformation by the constraints of a ring system. Comparisons with the corresponding *s-trans*-compounds are made. Compounds (I)—(VI) have been studied.

In earlier work, semiempirical CNDO/S calculations have been employed in the interpretation of p.e. spectra of oxamides.[1-3] This type of calculation is parametrized to fit electronic spectra and it has shown to be well suited to the prediction of p.e. spectra using the negative of the calculated molecular orbital (MO) energies as an approximation to the ionization potentials (Koopmans' theorem). The success of the CNDO/S method in reproducing p.e. spectra implies that the deficiencies in Koopmans' theorem, *i.e.* its neglect of electron re-



(I) $R^1 = R^2 = H$
(II) $R^1 = H, R^2 = CH_3$
(III) $R^1 = R^2 = CH_3$

(IV) a; R = H b; R = CH_3



(V) a; R = H b; R = CH_3 (VI) a; R = H b; R = CH_3

organization energy in the molecular ion and of differences in correlation energies between the ground state molecule and the ion, to some extent are taken care of by the parametrization. Furthermore, this implies that

the MO energies and the order of the MOs, as calculated by CNDO/S and similar methods, do not necessarily refer to the ground state of the molecule. It is thus to be expected that in some cases the order of the MOs in the ground state may be different from the order of the ionization events observed in the p.e. spectrum and assigned to these orbitals.[15]

In this work we have employed *ab initio* calculations to obtain MO energies. In order to calculate ionization energies for comparisons with experimental values from p.e. spectra, we have made empirical corrections for reorganization and correlation effects. This approach has been successful in earlier studies.[16,17] In this way we hope to be able to predict both the order and the energies of the MOs in the ground state *and* the order and energies of ionization events, as they show up in the p.e. spectra.

The purposes of the present work are as follows: (i) to investigate the ability of the computational approach used to support the interpretation of p.e. spectra of oxamides, (ii) to study the influence of conformations of oxamides on the ionization energies in p.e. spectra, and (iii) to evaluate the dependence of the ionization energies on the ring size of cyclic *s-cisoid* oxamides.

EXPERIMENTAL AND COMPUTATIONS

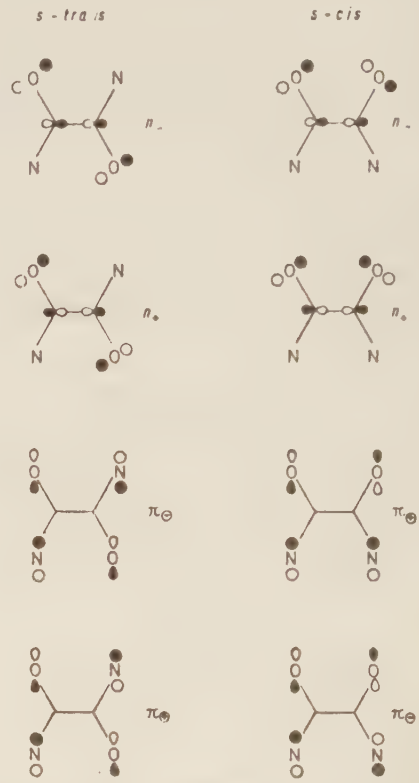
Photoelectron Spectra.—P.e. spectra were recorded on a Perkin-Elmer model PS-18 photoelectron spectrometer. The ionization energy was provided by the He^{I} (21.22 eV) resonance line. The range of temperatures used for solid samples was 53—150 °C. Spectra were calibrated with regard to energy and resolution using the $^2P_{3/2}$ line (12.13 eV) of Xe and the $^2P_{3/2}$ line (15.76 eV) of Ar. No decomposition of any molecule studied in this work was observed under the experimental conditions described above.

Synthesis.—Tetramethyloxamide (III) was prepared according to Persson and Sandström.[18] The synthesis of compounds (IVb), (Va), (Vb), and (VIb) will be described elsewhere.[14]

Calculations.—The *ab initio* calculations were carried out using the computer program MOLECULE.[19] For carbon, nitrogen, and oxygen, a Gaussian basis set of seven *s*-type and three *p*-type functions contracted to two and one, respectively, was used (a minimal basis). The basis set for hydrogen was made up from four Gaussian *s*-type functions contracted to one. Calculations on oxamide (I) were also performed with a contraction to a 'split shell' basis with four *s*-type and two *p*-type orbitals for carbon, nitrogen, and oxygen and two *s*-type orbitals for hydrogen. Orbital exponents and contraction coefficients were those given by Clementi *et al.* (C, N, O; 7/3 basis set)[20] and Huzinaga (H).[21] In the latter case a scaling factor of 1.34 was used.

The MOs have been classified according to the notation introduced by McGlynn *et al.*[1] The MOs discussed in this work and denoted n_+, n_-, $\pi_\oplus$, and $\pi_\ominus$ are shown in the Scheme. MO energies were converted into ionization energies as described in detail below.

Geometries.—The oxamide molecule has been studied by *X*-ray diffraction,[10] but for the remaining compounds investigated in this work no experimental geometries are available. Geometries used in the calculations were constructed from those of analogous molecules. As a starting point, the *X*-ray structure of oxamide was modified in order to make the geometry more appropriate for the gas phase. Strong hydrogen bonding in the crystalline state significantly influences the geometric parameters of this molecule. The modifications made were guided by observed



SCHEME

differences in structural parameters between *X*-ray [22] and electron diffraction [23] geometries of amides. The intercarbonyl bond length was given a value close to that of the corresponding bond length of glyoxal [24] and biacetyl [25] in

TABLE 1

Geometries used in the *ab initio* calculations [a]

Bond lengths (Å)		Bond angles (°)	
C_{sp^2}–C_{sp^2}	1.52	CCO	123, 126 [b]
C=O	1.22	C_{sp^2}–C_{sp^2}–N	115, 106 [b]
C_{sp^2}–N	1.36	C_{sp^2}–N–H	120
N–H	1.02	C_{sp^2}–N–C_{sp^3}	120, 112.3, [b] 126.5 [c]
N–C_{sp^3}	1.46, 1.44 [b]	H–C_{sp^2}–N	109.5
C–H	1.09	C_{sp^2}–C_{sp^2}–N	110
C_{sp^3}–C_{sp^3}	1.54		

[a] The symmetries used for the cyclic compounds were: C_{2v} for (IVa), C_s for (Va) and (VIa), with CO–CO dihedral angles of 0, 20, and 60°, respectively. All amide units were kept planar. [b] Used for (IVa). [c] Used for (Va).

the gas phase, and bond angles were modified to values appropriate for the *s-cis*-conformation.[26]

The structural parameters for the oxamide unit thus constructed were kept as unchanged as possible in the evaluation of the geometries for the cyclic compounds. The remaining parameters for the ring systems were estimated from standard values and from analogous ring compounds. The final geometries are given in Table 1. As shown below, moderate changes of the geometric parameters have an insignificant effect on the calculated orbital energies.

RESULTS

For *s-trans*-oxamide (I), using a minimal basis, the highest occupied MO is calculated to be $\pi_{\oplus}$, but the three MOs $\pi_{\oplus}$, n_+, and $\pi_{\ominus}$ are almost degenerate (Table 2). The n_- orbital is significantly more stable. The MO order in *s-cis*-oxamide is calculated to the $\pi_{\ominus}$, n_+, $\pi_{\oplus}$, and n_- (Table 2), with a larger separation between $\pi_{\oplus}$ and $\pi_{\ominus}$ and a smaller separation between n_+ and n_- than was found for the *s-trans*-conformation. The dependence of the MO energies on twisting around the intercarbonyl bond is shown in Figure 1.

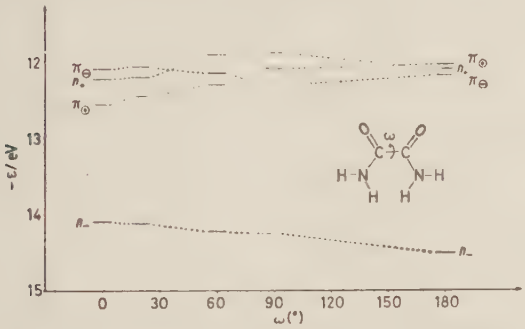


FIGURE 1 Dependence of orbital energies on dihedral angle for oxamide (I)

Using the more extensive 'split-shell' basis set, all four MOs increase in energy by approximately the same amount, *ca.* 1 eV (Table 2), leaving the separations between the orbitals essentially unchanged and the orbital order unaffected. The same result is observed for *s-cis* and 90° twisted oxamide (Table 2). These results justify our use of the minimal basis set for all other calculations described in this work to economize on computer time. The calculated MO energies are given in Table 2. To obtain an estimate of how possible deficiencies in the constructed geometries of the cyclic compounds (IV)—(VI) would affect the computed energies, the sensitivity of these energies to moderate changes in geometrical parameters was investigated. A 0.02 Å change in the C–C or C–N bond lengths resulted in MO energy changes of < 0.1 eV. The same result was obtained when the CCO bond angle was increased by 5° or the CCN angle decreased by the same amount. Thus, the effects of moderate geometrical changes on the computed MO energies are apparently small. Conversion of MO energies to ionization energies requires corrections for reorganization energies in the molecular ion and for differences in correlation energies between the ground and ionized states. We have used an approach based on *ab initio* calculations,[16,17] which has been successfully employed in studies on the assignments of ionization events in p.e. spectra. The differences between calculated energies for the four highest occupied orbitals in *s-trans*-oxamide (I) (Table 2) and the corresponding ionization energies as observed and assigned by McGlynn *et al.*[3] (Table 3), were formed and used as empirical corrections to (the negative of) the calculated MO energies for other oxamide derivatives. The corrections thus obtained are n_+ −2.26, n_- −2.80, $\pi_{\oplus}$ −0.99, and $\pi_{\ominus}$ −1.69 eV. As discussed by Roos *et al.*,[17] the corrections should be constant for each orbital type throughout a series of similar molecules. Since the corrections are largely determined by the gross structure of the orbitals the corrections for $\pi_{\oplus}$ and $\pi_{\ominus}$ should be inverted for *s-cis*-

TABLE 2

Molecular orbital energies from *ab initio* calculations (eV)

Compound	n_+	$\pi_{\ominus}$	$\pi_{\oplus}$	n_-
(I) *s-trans*	12.06	12.14	12.03	14.52
(I) *s-trans* [a]	11.18	11.13	11.06	13.52
(I) 90°	11.87	12.31	12.06	14.26
(I) 90° [a]	10.95	11.42	11.15	13.15
(I) *s-cis*	12.23	12.10	12.55	14.09
(I) *s-cis* [a]	11.36	11.20	11.57	12.85
(II) *s-trans*	12.02	11.69	11.52	14.48
(IVa)	12.02	12.49	11.73	14.69
(Va)	12.20	11.26	12.13	14.11
(VIa)	11.78	11.40	11.55	13.89

[a] 'Split-shell' basis. Otherwise a minimal basis set was used.

TABLE 3

Calculated and experimental ionization energies for compounds (I)—(VI)

Compound	MO	Calculated (eV)	Experimental (eV)	
(I)	n_+		9.80 [a]	
	$\pi_{\ominus}$		10.50	
	$\pi_{\oplus}$		11.04	
	n_-		11.72	
(II)	n_+		9.33 [a]	
	$\pi_{\ominus}$		9.62	
	$\pi_{\oplus}$		10.07	
	n_-		11.20	
(III) [b]	n_+	8.70	8.9—9.2	9.02 [a]
	$\pi_{\oplus}$	8.87		9.34
	$\pi_{\ominus}$	9.24		9.08
	n_-	10.38	10.5	10.49
(IVa)	n_+	9.76		
	$\pi_{\oplus}$	10.04		
	$\pi_{\ominus}$	11.50		
	n_-	11.89		
(IVb)	$\pi_{\oplus}$	9.16	9.3—9.5	
	n_+	9.29		
	$\pi_{\ominus}$	10.53	10.7	
	n_-	11.37	11.5	
(Va)	n_+	9.94	9.70	
	$\pi_{\ominus}$	10.27	10.20	
	$\pi_{\oplus}$	10.44	10.55	
	n_-	11.31	11.70	
(Vb)	$\pi_{\ominus}$	9.30	9.20	
	n_+	9.47	9.30	
	$\pi_{\oplus}$	9.56	9.60	
	n_-	10.79	10.35	
(VIa)	n_+	9.52		
	$\pi_{\oplus}$	9.86		
	$\pi_{\ominus}$	10.41		
	n_-	11.09		
(VIb)	$\pi_{\oplus}$	8.98	8.8—9.2	
	n_+	9.05		
	$\pi_{\ominus}$	9.44		
	n_-	10.57	10.5	

[a] Ref. 2. Assignments based on CNDO/S calculations. [b] The carbonyl–carbonyl bond 60° twisted.

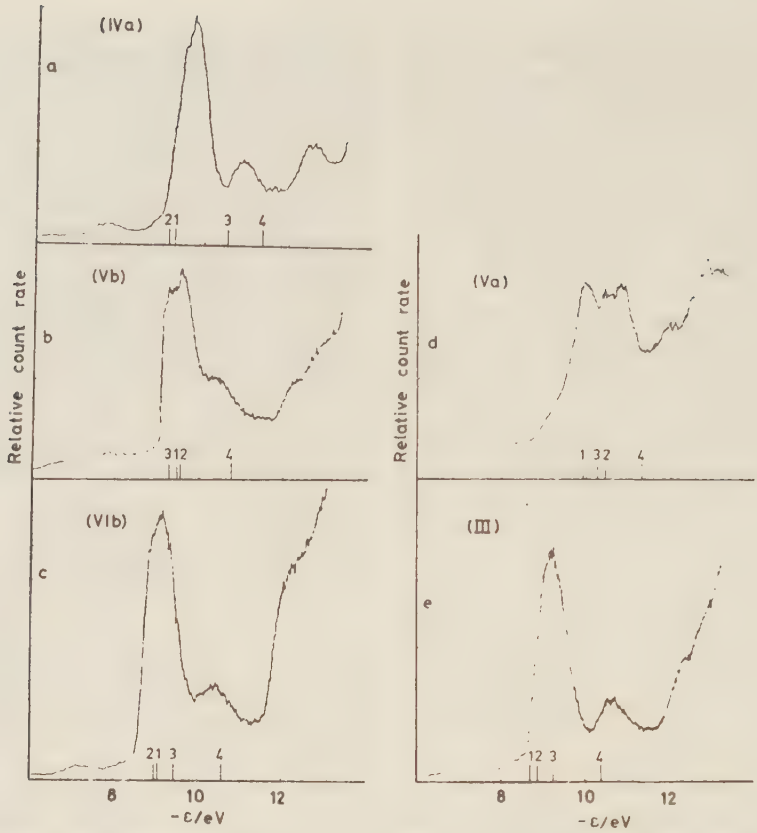


FIGURE 2 Photoelectron spectra of compounds (III), (IVb), (Va and b), and (VIa). Vertical bars indicate calculated ionization energies. The numbers above the bars indicate orbital type: $1 = n_+$, $2 = \pi_\oplus$, $3 = \pi_\ominus$, and $4 = n_-$

oxamides. Inspection of the Scheme shows that the gross structure of the $\pi_\oplus$ orbital of the *s-trans*-conformer is similar to that of the $\pi_\ominus$ orbital of the *s-cis*-conformer and *vice versa*. The approach described above is based on the assumption that variations in ionization energies in a series of similar molecules are reflected in the variations of MO energies. This justifies the use of the same notation for orbital and ionization energies.

It is interesting to note that the differences between the MO energies for *s-trans*-oxamide (Table 2), calculated by the 'split-shell' basis set, and the corresponding experimental ionization energies (Table 3) are very similar to those obtained by Roos *et al.* in their studies on azabenzenes [17] and anhydrides,[16] using a similar basis set. This implies, as discussed by Roos *et al.*,[16] that empirical corrections obtained from studies on one class of molecules may be used for other classes as well, provided that the calculations are being done with basis sets of approximately the same quality.

All calculations in this work, except for compound (II), were done for the *N*-unsubstituted parent compounds. The MO energies were converted to ionization energies as described above. *N*-Methylation effects were taken into account using the *N*-methyl shifts determined by McGlynn *et al.* (n_+ −0.47, n_- −0.52, $\pi_\oplus$ −0.97, and $\pi_\ominus$ −0.88 eV), with $\pi_\oplus/\pi_\ominus$ inversion for *s-cis*-compounds.[3] These shifts have proved to be remarkably constant and additive for amides and oxamides.[1] Experimental and calculated ionization energies are summarized in Table 3. Experimental p.e. spectra in the 8—12 eV region are shown in Figure 2 with the calculated ionization energies and their assignments indicated by vertical bars.

The p.e. spectra of most of the compounds studied show extensively overlapped bands. The spectrum of (Va) is however quite well resolved and may be used as a test case for the approach described above. The calculated ionization energies agree very well with the experimental ones, especially for the three lowest ionization events (see Figure 2d and Table 3). *N*-Methylation shifts all ionizations towards lower energies, but the $\pi_\oplus$ and $\pi_\ominus$ bands are more sensitive to the alkylation effect than the n_+ and n_- bands.[3] This results in a strong overlap of the n_+, $\pi_\oplus$, and $\pi_\ominus$ bands in the p.e. spectra of (Vb) (Figure 2b). It is clearly a great advantage to be able to study the *N*-unsubstituted compounds of this class of molecules, since the p.e. spectra are more resolved with less *N*-substitution. However, all attempts to synthesize compounds (IVa) and (VIa) have failed so far.[14] The calculated ionization energies for these compounds, as given in Table 3, thus constitute a prediction of their p.e. spectra.

DISCUSSION

As mentioned in the introduction, the order of MO energies does not need to be the same as the order of ionization energies. For *s-trans*-oxamide (I) the MO order is $\pi_{\oplus}$, n_+, $\pi_{\ominus}$, and n_- (Table 2), while the experimental order of ionization energies is n_+, $\pi_{\ominus}$, $\pi_{\oplus}$, and n_- (Table 3). In this case, however, the three highest occupied MOs are nearly degenerate. The case of (Va) is more clear cut. For this molecule, the calculated MO order is $\pi_{\ominus}$, n_+, $\pi_{\oplus}$, and n_-, with a significant separation between $\pi_{\ominus}$ and $n_+/\pi_{\oplus}$. Due to differences in correction terms for orbitals of π- and σ-type (see above), the order of the $\pi_{\oplus}$ and n_+ processes is reversed in the experimental p.e. spectra. Great caution should thus be exercised if conclusions about the order of MO levels are to be drawn from p.e. spectra. Since CNDO/S calculations reproduce p.e. spectra very well, the same caution applies to conclusions drawn from such calculations.

N-*Methyl Shifts*.—The observed *N*-methyl shifts for oxamides are close to 0.5 eV for n_+ and n_- and 0.9—1.0 eV for $\pi_{\oplus}$ and $\pi_{\ominus}$.[3] This difference is expected, since the *n* orbitals are largely localized on oxygen, with small amplitudes on nitrogen. In contrast, the $\pi_{\oplus}/\pi_{\ominus}$ orbitals have large amplitudes on nitrogen. CNDO/S calculations on oxamides give a fair account of the *N*-methyl effect.[3] However, the *ab initio* calculations employed in the present work show almost no shift of the *n* orbitals when calculations on oxamide and *NN'*-dimethyloxamide are compared. The energies of the $\pi_{\oplus}/\pi_{\ominus}$ levels is, on the other hand, increased by *ca.* 0.5 eV (Table 2). These calculated *N*-methyl shifts are thus *ca.* 0.5 eV smaller than the effects observed on ionization energies in p.e. spectra. Although these differences between calculated and experimental values may to some extent be due to the limited basis set used in the calculations, they more probably imply that the effects of *N*-methyl substitution on p.e. spectra of oxamides (and other classes of compounds as well) are a composite of changes in MO energies and changes in reorganization and correlation energies.

Conformation of Oxamides and its Influence on P.e. Spectra.—The p.e. spectra of *s-trans-NN'*-dimethyloxamide (II) and its cyclic *s-cis*-analogue (Va) show significant differences (Table 3). Although the order of ionization events (n_+, $\pi_{\ominus}$, $\pi_{\oplus}$, and n_-) is the same for the two molecules, the ionization energies in the 9—12 eV region are increased by 0.4—0.6 eV on going from (II) to (Va). These differences are not those expected for a conformational effect on going from *s-trans* to *s-cis*. CNDO/S calculations indicate small conformational effects, < 0.1 eV, on the n_+ and $\pi_{\ominus}$ levels. The $\pi_{\oplus}$ and n_- levels are somewhat more affected, showing shifts of +0.2 and −0.3 eV respectively.[8] CNDO/2 Calculations give exactly the same results.[27] *Ab initio* calculations give somewhat larger differences (see Figure 1 and Table 2), but again the n_+ and $\pi_{\ominus}$ MOs are less influenced by the *s-trans–s-cis* conversion than are the $\pi_{\oplus}$ and n_- levels. Also in this case the energy changes of the two latter MOs have different signs.

Calculations of ionization energies of *s-trans* (II) and *s-cisoid* (II) [20° twisted as in (Va)], including reorganization and correlation terms, result in the following shifts on the ionization energies on going from *s-trans* to *s-cisoid* (20°): n_+ +0.01, $\pi_{\oplus}$ −0.27, $\pi_{\ominus}$ +0.70, n_- −0.4 eV. It is clear that the observed differences in the spectra of (II) and (Va) cannot solely be interpreted in terms of effects due to conformational changes. The observed shifts must be a composite of a conformational effect and an effect due to differences between two *N*-methyl groups and an ethylene bridge. This effect, however, is not to be found in the energies of the MO levels. The n_+/n_- and the $\pi_{\oplus}$ levels in (II) and (Va) have very similar energies (Table 2). The $\pi_{\ominus}$ MO lies *ca.* 0.5 eV higher in (Va) than in (II) depending on the CH_2–CH_2 antibonding character of this orbital in (Va). Instead, differences in the reorganization and correlation term necessary to convert MO energies to ionization energies must be invoked. It should be noted that the procedure used in the present work very satisfactorily reproduces the p.e. spectrum of (Va). This implies that the correction terms evaluated from p.e. spectra and *ab initio* calculations of oxamide (I) are also valid for the cyclic *s-cisoid*-oxamides, that is no extra terms due to the alkyl bridges need be included. As discussed above this is not the case for MO levels if methyl groups are included in the MO calculations. This analysis indicates a serious problem in studies of unstable or low population conformers by p.e. spectroscopy. A common technique for such studies is the preparation of model compounds in which the desired geometrical or conformational properties are introduced by rigidly fixing part of the molecule by alkyl bridges. This may lead to a complete masking of the desired effect, by the influence of the bridging alkyl part, as in the case described above. In such cases conclusions drawn from p.e. spectra may be totally misleading.

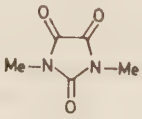
Ring Size and Ionization Energies.—Compounds (IVb)—(VIb) form a series of molecules with increasing twist around the intercarbonyl bond. Compound (IVb) is probably planar or close to planar. Models and analogous ring compounds suggest that the twisting in (Vb) and (VIb) is *ca.* 20 and 60°, respectively. As indicated by the assignments in Figure 2, the five-membered ring compound (IVb) is quite different from the other two and will therefore be dealt with separately.

The p.e. spectra of (Vb) and (VIb) are quite similar (Figures 2b and c), the main difference being a small but significant shift of the low energy band towards lower ionization energies as the ring size increases. This may be due to a corresponding increase in the intercarbonyl dihedral angle and/or to differences in the lengths of the alkyl parts of the ring systems. *Ab initio* calculations including the correction terms described above nicely reproduce the difference in p.e. spectra between (Vb) and (VIb) (Table 3) but the picture that emerges is not a simple one. The three ionization events making up the low energy band all qualitatively behave as expected for an increasing twist of the oxamide unit. According to

calculations summarized in Figure 1, the energies of the n_+ and $\pi_\oplus$ levels increase on going from a 20 to a 60° twist. A small decrease in the energy of the $\pi_\ominus$ level is also expected. These changes show up somewhat enlarged in the calculations of ionization energies of (Vb) and (VIb). However, according to calculations on oxamide (Figure 1), the n_- level should exhibit a decrease in energy with increasing twist. Calculations on (Vb) and (VIb) show an increase in the energy of the n_- level. It is thus clear that differences in the inductive effects of the alkyl parts of the ring system influence the p.e. spectrum to some extent.

This may also be seen in the calculated MO energies of (Va) and (VIa) (Table 2). The differences in energies, especially for the n_+ and $\pi_\oplus$ levels, are about twice as large as the corresponding differences between 20 and 60° twisted *s-cis*-oxamide. The conclusion is that the shifts observed in the p.e. spectra of (Vb) and (VIb) are about equally due to conformational changes and to differences in alkyl inductive effects. The p.e. spectrum of tetramethyloxamide (III) shows a further shift of the low-energy band towards lower ionization energies than does (VIb). This shift is also reproduced by the calculations (Table 3), using the MO energies for 60° twisted oxamide and adding corrections for methyl groups. Since identical geometries and dihedral angles were employed in the calculations of ionization energies for (III) and (VIb), the observed shifts must be interpreted as a differential influence of the *N*-alkyl substituents.

NN'-*Imidazolidine-4,5-dione* (IVb).—This compound may be viewed as a model for a planar *s-cis*-oxamide unit. The geometry is quite different from that of oxamide itself (Table 1), but the main differences are to be found in the bond angles, and these differences, as shown above, are not expected to influence the p.e. spectrum to a significant degree. In contrast to the other oxamide derivatives studied in this work, the low-energy ionization band is calculated to consist of only two ionization energies, $\pi_\oplus$ and n_+, with the $\pi_\ominus$ event of considerably higher energy. This conclusion is supported by the analysis of the p.e. spectrum of *NN'*-dimethylimidazolidine-2,4,5-trione (VII) by McGlynn *et al.*[3] For this



(VII)

related compound, the first band in the p.e. spectrum is also due to the $\pi_\oplus$ and n_- ionization processes, with the $\pi_\ominus$ process *ca.* 0.7 eV higher in energy. Although the p.e. spectra of (IVb)—(VIb) are quite similar, the assignments of the two bands in the 8—12 eV region show important differences. The reason for the unexpectedly high ionization energy of the $\pi_\ominus$ process lies in the nodal properties of the corresponding MO. This orbital possesses a node at the methylene group making it quite insensitive to changes at this position. The ionization energy, 10.5 eV, is thus close to that observed for (VII) (10.97 eV).[3]

Conclusions.—Ionization energies in p.e. spectra of cyclic *s-cisoid*-oxamides are remarkably well accounted for by MO energies from *ab initio* calculations, empirically corrected for reorganization and correlation effects. The influence of the alkyl parts of the cyclic ring systems necessary to force the oxamide unit into *s-cisoid*-conformations seriously masks the effects of conformational change. A qualitative picture of the degree of twist of the oxamide unit in different ring compounds may be obtained, but differential effects due to different lengths of cyclic alkyl chains prohibits a more quantitative analysis.

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PAPER IV

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Running titles: Henriksen, Isaksson, Liljefors and Sandström
UV and UP Spectra of Thiooxamides

Ultraviolet Absorption and Photoelectron Spectra of Some Cyclic and Open-chain Mono- and Dithiooxamides

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A series of dithiooxamides with dihedral angles of ca 90°, 65° and 30° between the thioamide chromophores have been studied by ultraviolet photoelectron and absorption spectroscopy. Assignment of ionizations and absorption bands have been made on the basis of previous CNDO/S and ab initio calculations of orbital and transition energies in the analogous oxamide systems. The assignments in the photoelectron spectra have been corroborated by a study of some monothiooxamides.

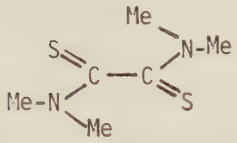
The ultraviolet-visible absorption spectra of thiocarbonyl compounds in general and of thioamides in particular have been studied over a long period of time.[1-5] More recently, the absorption spectroscopic studies have been supplemented with investigations of ultraviolet photoelectron spectra.[6-8] One reason for this interest may be the fact that these compounds often present well resolved transitions, which appear in an easily accessible wavelength region and which are sensitive to substituents and solvents in a way which makes them suitable for testing theoretical

calculations on various levels of approximation. Another reason may be found in the usefulness of thioamides as qualitative electronic models for amides. A certain parallelism can be expected between the energy levels and transitions in these two groups of cromophores, but the amide chromophore is much less accessible to studies because of the high energies and the closeness of its transitions.

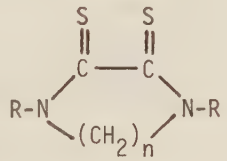
Several years ago, one of us[9] studied the ultraviolet - visible absorption spectra of mono- and dithiooxamides, and it was concluded that N,N,N',N'-tetraalkyl derivatives are so strongly twisted about the pivot bond that the thioamide parts appear as essentially isolated chromophores. This result was later corroborated by emission spectroscopy[10] and by dynamic NMR spectroscopy[11], and dipole moments were recorded which were in agreement with twist angles close to 90°.[12] N,N,N'-Trialkyl derivatives also appear twisted, whereas N,N'-disubstituted and less substituted compounds seem to prefer a nearly planar s-trans conformation, as evidenced by the low dipole moments for some representative compounds.[12]

The present work was undertaken to study the rôle of the dihedral angle about the pivot bond in determining the orbital and transition energies in dithiooxamides. N,N,N',N'-Tetramethyldithiooxamide (I) was chosen as a model for a system with perpendicular thioamide groups. In the cyclic compounds (II) the dihedral

angle depends on the length of the bridge. According to molecular mechanics calculations,[13] the angle is 62° in the seven - membered ring compounds IIa and IIb, and 31° in the six - membered compound IIc.



I



IIa: R = Me, n = 3
b: R = iPr, n = 3
c: R = Me, n = 2

EXPERIMENTAL: The preparation of the compounds is described elsewhere.[9,14,15] The photoelectron spectra (UPS) were recorded with a Perkin-Elmer Model PS-18 photoelectron spectrometer, employing the He (I) 21.22 eV resonance line for ionization. The spectra were calibrated with respect to energy and resolution with aid of the ^2P 3/2 line (12.13 eV) of Xe and the $^2P_{3/2}$ line (15.76 eV) of Ar. No decomposition of any molecule studied in this work was observed under the experimental conditions. The vertical ionization potentials are reported in Figure 1.

Figure 1

The ultraviolet spectra were recorded with Cary Model 15 and Cary Model 219 spectrometers. For identification of $n \rightarrow \pi^*$ transitions, spectra should preferably have been recorded in a completely nonpolar solvent, such as cyclohexane, and in pure ethanol. However, due to

solubility problems varying proportions of chloroform had to be employed also in the most dilute solutions (ca 10^{-5}M). The solvents used, and the positions and extinction coefficients of the absorption maxima are reported in Table 1. Some representative spectra are shown in Figure 3.

Table 1

Figure 3

RESULTS AND DISCUSSION

The notion of a complete isolation of the thioamide chromophores in a 90° twisted dithiooxamide like I is not valid. A simple argument based on through - bond interaction, assuming mainly p character for the sulphur lone pairs (n) shows that these may interac quite strongly by intervention of the σ-orbitals in the C-C bond. To a first approximation, the splitting caused by this interaction should be independent of the dihedral angle. Larson and McGlynn[16] performed CNDO/S calculations with CI on oxamide for the dihedral angles 0°, 45°, 90°, 135°, and 180°, and they found a splitting of the n levels into a higher symmetric (n_{+}) and a lower antisymmetric (n_{-}) combination (Scheme 1), with energies rather insensitive to the dihedral angle and with a splitting of ca 2.3. eV. Ionizations assignable to these orbitals have been observed in the photoelectron spectra of several oxamides.[17-19] Two of us[19] have performed a photoelectron spectroscopic investigation of cyclic oxamides combined with *ab initio* calculations, and the results agree with those of McGlynn *et al*. as far as the splitting of the n levels is concerned.

Scheme 1

The photoelectron spectra (UPS) of the dithiooxamides in general display a group of more or less overlapping bands in the ionization potential (IP) region 7.5 to 8.7 eV. At most three resolved bands are observed, but the intensities clearly reveal that four ionization events are present. By comparison with the analogous oxamides,[16,18,19] these can be ascribed to the n_-, n_+, $\pi_\oplus$ and $\pi_\ominus$ levels (Scheme 1). The splitting of the n levels in the oxamides is of the order of 1.0-1.7 eV.[18,19] The overlap between the sulfur lone pairs and the σ-orbital in the pivot C-C bond is smaller than the corresponding overlap in the oxygen analogues, whereas the energy gap between these orbitals is greater in the dithio analogues. Therefore the splitting of the n levels can be expected to be significantly smaller in the latter compounds. The higher energy of the sulfur valence orbitals compared to the oxygen orbitals contributes to raise the energies of the n and π orbitals which have contributions from sulfur basis orbitals.

In N,N,N',N'-tetramethyloxamide, the ionizations are assigned, from low to high ionization potentials to the n_+, $\pi_\ominus$, $\pi_\oplus$, and n_- levels. The UPS of I shows a sharp band at 7.75 eV, a somewhat broader one at 8.03 eV, and a more intense one, evidently due to two ionization events, at 8.50 eV. Both the bandshapes and analogy with the oxamide permit the alternative assignments: n_+, $\pi_\oplus$, $\pi_\ominus$, n_- and n_+, $\pi_\ominus$, $\pi_\oplus$, n_- from low to high IP:s. An analysis of the effect of changing the dihedral angles permits a more precise assignment. In the spectrum of IIa, only two bands are observed below 10 eV, one at 7.83 eV and the other one at 8.50 eV. The reduction of the dihedral angle by ca 30^0 from I should according to the ab initio calculations in Ref. 19 result in a decrease in the n_+-n_- splitting, a lowering of the $\pi_\oplus$ level, and a raising of the $\pi_\ominus$ level. Therefore, the band at 7.83 eV is ascribed to ionizations from the n_+ and $\pi_\ominus$ levels, and the one at 8.50 eV to ionizations from the $\pi_\oplus$ and n_- levels. Consequently, the order of IP:s in I should be the same one as may be calculated

for a 90° twisted N,N,N',N'-tetramethyloxamide from data in Ref. 19, i.e. with the π_{θ} level at higher energy (lower IP) than the $\pi_{\oplus}$ level.

The notation $\pi_{\oplus}$ and π_{θ} may seem questionable for I, where the two thioamide groups are nearly orthogonal, but due to different interactions with other orbitals of suitable symmetry the two orbitals remain different, and it is possible to keep track of them in the calculations over an entire 180° rotation.

The assignments for IIa are corroborated by a study of the N,N'-diisopropyl analogue IIb. The inductive electron donating (+I) effect of the iPr group is slightly greater than that of Me, and it has been observed both in the formamide[20] and thioformamide[7,21] series that the highest π level is raised more strongly than the n level when the +I effect of the N substituent is increased. In agreement with this, shifts on N,N'-dimethylation in oxamides of ca 0.5 eV for n_{+} and n_{-} and of 0.9-1.0 eV for $\pi_{\oplus}$ and π_{θ} have been observed.[18] In the UPS of IIb, the exchange of Me for iPr results in a shift to lower IP:s of all bands under discussion. The band at 7.83 eV in the spectrum of IIa is replaced by two at 7.53 and 7.68 eV, which are assigned to π_{θ} and n_{+} respectively. The remaining broad band with a peak at 8.20 eV and a shoulder at 8.3 eV is assigned to a superposition of $\pi_{\oplus}$ and n_{-}.

A further reduction of the dihedral angle should lead to an increase of the π_{θ} and n_{-} energies and a decrease of the $\pi_{\oplus}$ and n_{+} energies.[19] This seems to be realized in the six-membered dithioxamide IIc. The spectrum in the 7-9 eV region is not well resolved, but it shows clear peaks at 7.82 and 8.66 eV, separated by a broad band

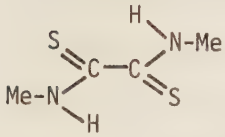
with diffuse peaks at 7.9 and 8.1 eV. The most likely assignment is one of π_θ, n_-, n_+, $\pi_\oplus$ and π_θ, n_+, n_-, $\pi_\oplus$ from low to high IP:s.

Generally, the interpretation of the observed IP:s in terms of the interactions between n and π orbitals varying with the dihedral angle is more straightforward for the dithiooxamides than for the corresponding oxamides. In the latter group, the observed deviations were explained in terms of interactions between the orbitals in the amide chromophores and those in the saturated parts of the molecules.[19] It is natural that these interactions should be less important in the dithiooxamides, where the energy gap between the n and highest π orbitals on one hand and the C-C σ orbitals on the other is ca 1.5 eV greater.

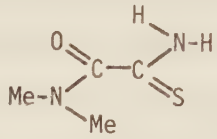
The ab initio calculations on the oxamide system referred to above[19] predict a crossing over of the π_θ and $\pi_\oplus$ levels between the dihedral angles 60° and 90°, and a slight raising of the energies of both levels with increasing dihedral angle. Simultaneously, both n levels are lowered, and in s-trans oxamide the calculated order of the levels, from high to low energy, is $\pi_\oplus$, n_+, π_θ, and n_-. N,N'--Dimethyldithiooxamide (III) is probably close to the s-trans form. Its UPS displays sharp bands at 8.23 and 8.59 eV and a broader band, evidently due to two ionization events, at 9.03 eV. These bands appear to correspond closely to those of I, though all bands of III are displaced by ca 0.5 eV to higher IP:s. However, the arguments given above show that one cannot safely make the same assigment for the two compounds, i.e. n_+, π_θ, and ($\pi_\oplus$ + n_-) with increasing IP. If only the N-methylation shift had been operating, the increments given above should lead to the prediction 8.25 eV (n_+), 9.00 eV (n_-),

9.03 eV (π_θ) and 9.50 eV ($\pi_\oplus$). In the oxamide system, the calculated effect of changing the dihedral angle from 60° to 180° is to raise the $\pi_\oplus$ level by 0.4 eV, to leave the π_θ level unchanged, and to lowe the n_+ level by 0.2 eV and the n_- level by 0.3 eV. If we add these effects to the N-methylation shifts we arrive at the assignment n_+, π_θ, ($\pi_\oplus$ + n_-), i.e. the same as for I.

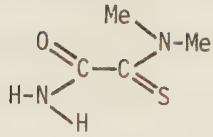
In monothiooxamides, the n and π levels have rather different energies in the two chromophores, and a much weaker interaction



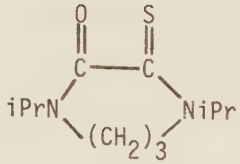
III



IV



V



VI

should be expected. In fact, the UPS of N^o,N^o-dimethylmonothiooxamide (IV) and its N^s,N^s analogue (V) are surprisingly well reproduced by adding the UPS of thioformamide and N,N-dimethylthioformamide and formamide (for V) respectively (Figure 2). The effects of coupling, i.e. the deviations from the component spectra, are clearly smallest in V, where the differences in energy are the largest. Also in the cyclic monothiooxamide VI, the ionizations at lowest energy are clearly split into one group of predominantly thioamide character (7.75 and 8.05 eV

Figure 2

and one of amide character (8.79 and 9.37 eV).

The ultraviolet absorption spectra cannot be profitably discussed on the basis of the energies of the ground state levels alone. However, Larson and McGlynn[16] have calculated the energies of the excited states of oxamide by the CNDO/S method with configuration interaction (CI) for several dihedral angles. A qualitative correspondence should be expected between the effects of the dihedral angle on the state energies for oxamides and dithiooxamides, and therefore we base our discussion upon these calculated state energies, part of which are shown in Scheme 2.

heme 2

The CI calculation on 90° twisted oxamide gave two $n\pi^{*}$ states, one corresponding to a transition at 179 nm with oscillator strength 0.01, and one at 364 nm with zero oscillator strength. The calculations also indicate a considerable splitting of the lowest $\pi\pi^{*}$ state except for dihedral angles around 90°, where a splitting of only 0.2 eV (1600 cm^{-1}) is calculated. The energies of the lowest $\pi\pi^{*}$ states are calculated to be quite similar in acetamide and in a 90° twisted oxamide.

Even if the calculated transition energies seem rather unrealistic, the splitting pattern should be correct. We can therefore expect the following transitions on a nearly 90° twisted dithiooxamide like I: One quite weak and one somewhat stronger $n\rightarrow\pi^{*}$ transition (to the $n_{+}\pi^{*}$ and $n_{-}\pi^{*}$ states) and two close-lying $\pi\rightarrow\pi^{*}$ transitions (to the $\pi_{o}\pi^{*}$ states, where π_{o} represents the highest bonding π orbital). The $n\rightarrow\pi^{*}$ transitions should fall above and below 365 nm, and the $\pi\rightarrow\pi^{*}$

transitions near 272 nm, these being the wavelengths of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions in N,N-dimethylthioformamide[3] (data from non--polar solvents). We observe (Figure 3 and Table 1) one band at ca 365 nm (ε = 530), which, because of its relatively high intensity, is ascribed to the transition to the $n_- \pi^*$ state. The transition to the $n_+ \pi^*$ state, being of much less intensity, is probably hidden under the 365 nm band. We also find two strong bands at 276 nm and 26 nm (ε = 17400 and 14900 respectively). Besides, a shoulder can be discerned on the long-wavelength side of the band at 276 nm, corresponding to a band at ca 295 nm with ε ca 6000 (the values in Table 2 are for the point of inflection on the curve). The separation between the two latter bands (0.29 eV) and their intensity relation are in reasonable agreement with those calculated for the two lowest $\pi \rightarrow \pi^*$ transitions (separation 0.20 eV and oscillator strengths 0.05 and 0.37 respectively),[16] and this assignment is therefore proposed. The band at 262 nm may be due to an $n \rightarrow \sigma^*$ transition in the thio-carbonyl groups. A band assigned to such a transition appears in the region 220-230 nm in spectra of simple thiocarbonyl compounds,[22] and the raising of one n level (n_+) by the coupling should lead to a bathochromic shift of this transition. The calculations in Ref. 16 (Scheme 2) indicate that the lowest $n\sigma^*$ state is considerably lower in the 90° twisted oxamide than in the s-cis and in particular in the s-trans form.

When the dihedral angle between the thioamide chromophores is reduced, as in IIa, the splitting of the pairs of $n\pi^*$ and $\pi\pi^*$ states should be larger. Four distinct $\pi \rightarrow \pi^*$ transitions should be possible, to the following states, from low to high energy: $\pi_\oplus \pi^*_+$, $\pi_\ominus \pi^*_+$, $\pi_\ominus \pi^*_-$, and $\pi_\oplus \pi^*_-$. Similarly, transitions to the $n_+ \pi^*_+$, $n_+ \pi^*_-$, $n_- \pi^*_+$, and $n_- \pi^*_-$

states are possible (Scheme 2). The two π_+^* states form a close-lying pair, as do the π_-^* states.

The spectrum of IIa displays a band at 392 nm (ε = 860), most likely due to the lowest $n_- \rightarrow \pi^*$ transition (or to both of them), i.e. corresponding to the 365 nm band in the spectrum of I. The two $n_+ \rightarrow \pi^*$ transitions, which should be considerably weaker, are probably hidden under the 392 nm band.

A band at 306 nm (ε = 8900) can be ascribed to a transition to the $\pi_\theta\pi_+^*$ state, corresponding to the band at 295 nm in I. Two bands at 278 nm (ε = 12700) and 240 nm (ε = 10800) are tentatively assigned to one $\pi\rightarrow\pi^*$ and one $n\rightarrow\sigma^*$ transition, in this order. Both bands show a slightly negative solvatochromy (2.5 and 4 nm from cyclohexane to ethanol) of about the order of magnitude found for $\pi\rightarrow\pi^*$ transitions in other thioamides,[23,24] whereas $n\rightarrow\sigma^*$ transitions in simple thioamides generally are more strongly affected.[24]

Diminishing the dihedral angle should lead to a further lowering of the $n_+\pi_+^*$, $n_-\pi_+^*$, and $\pi_\theta\pi_+^*$ states. In good agreement with this, the spectrum of IIc shows a weak band (ε = 43) as a shoulder at 480 nm, a region where IIa has no absorption. A somewhat stronger band, ascribed to the transition to the $n_-\pi_+^*$ state, appears at 412 nm (ε = 540), and a still stronger one (ε = 8400) at 312 nm is ascribed to the transition to the $\pi_\theta\pi_+^*$ state. In agreement with this assignment, the two weaker bands show strong negative solvatochromy. No further bands appear above ca 240 nm. The successive retreat of the $n\rightarrow\sigma^*$ band to shorter wavelengths in the series I, IIa, IIc is entirely in agreement with the calculated dependence of the energy of the $n_-\sigma^*$ state on the dihedral angle.[16]

Summing up, the effects on the UV spectra of changing the dihedral angle between the thioamide chromophores in dithiooxamides can be qualitatively explained by analogy with the corresponding effects in the oxamide system calculated by the CNDO/S-CI method.[16]

Acknowledgements. We are grateful to Dr. G. Pfister-Guillouzo Pau, and to Dr. J. Meeks,[25] then at Baton Rouge, for recording some of the photoelectron spectra. The Swedish authors also thank the Swedish Natural Science Research Council for financial support. The cost for the Perkin-Elmer PS-18 spectrometer at the H.C. Oerste Institute was defrayed by a grant from the Danish Natural Science Research Council.

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Table 1. Ultraviolet spectra of dithiooxamides.

Compound	Solvent[a]	$n \rightarrow \pi^*$				$\pi \rightarrow \pi^*$				$n \rightarrow \sigma^*$	
		λ_{max} nm	ε	λ_{max} nm	ε	λ_{max} nm	ε	λ_{max} nm	ε	λ_{max} nm	ε
I	A	365	530			ca 295 s[b]	ca 9000	276	17400	260	14900
	B	345 s	500			ca 295 s	ca 9000	272	20500	260 s	17800
IIa	A	392	860			306	8900	278	12700	240	10800
	B	382	1090			306	11200	274	12400	238	11800
IIc	A	480 s	43	412	540	312	8400				
	B	470 s	75	400	880	316	11500				

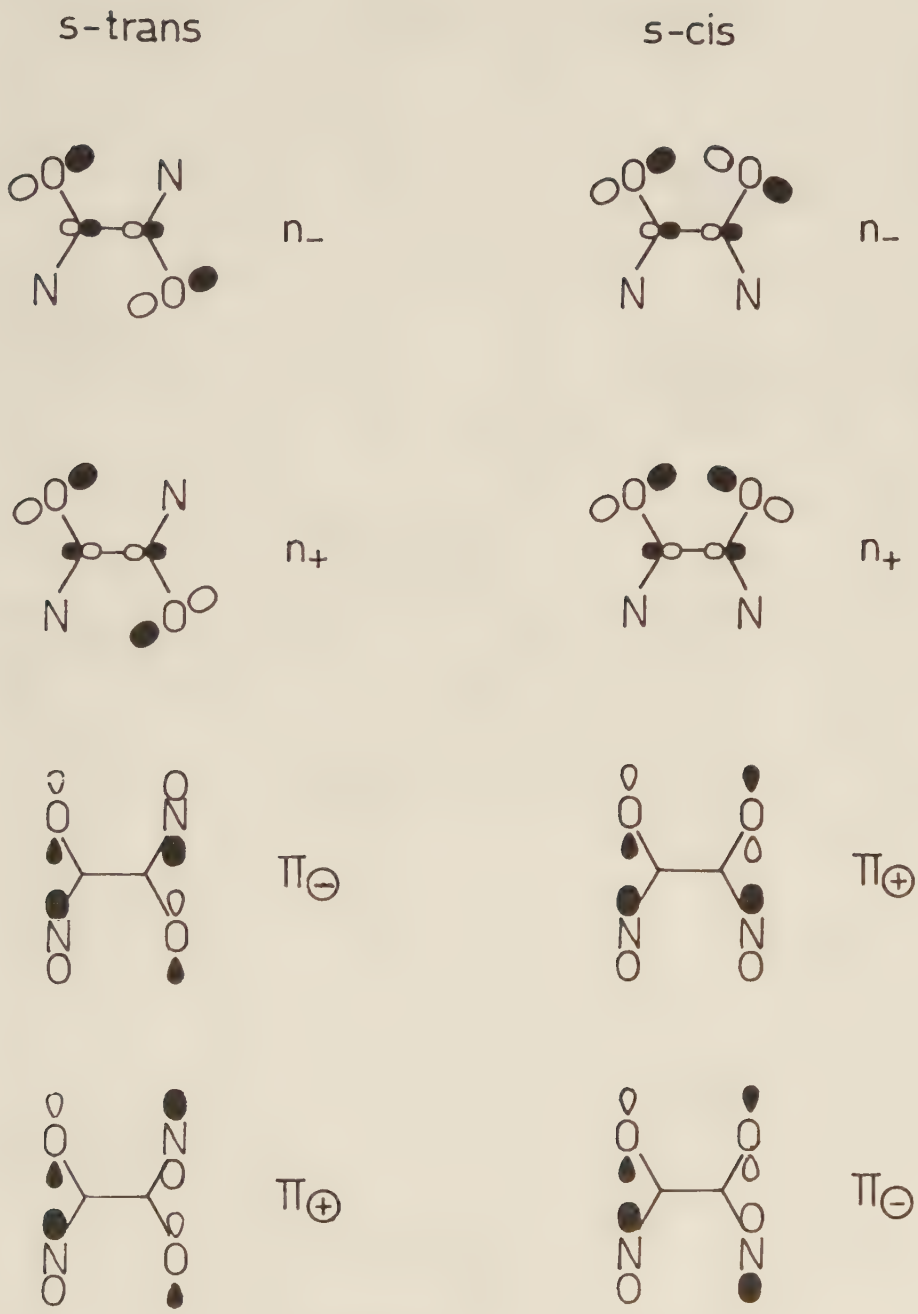
[a] A = chloroform-cyclohexane 3:7 (v/v). B = chloroform-ethanol 3:7 (v/v). [b] Shoulder.

Figure captions

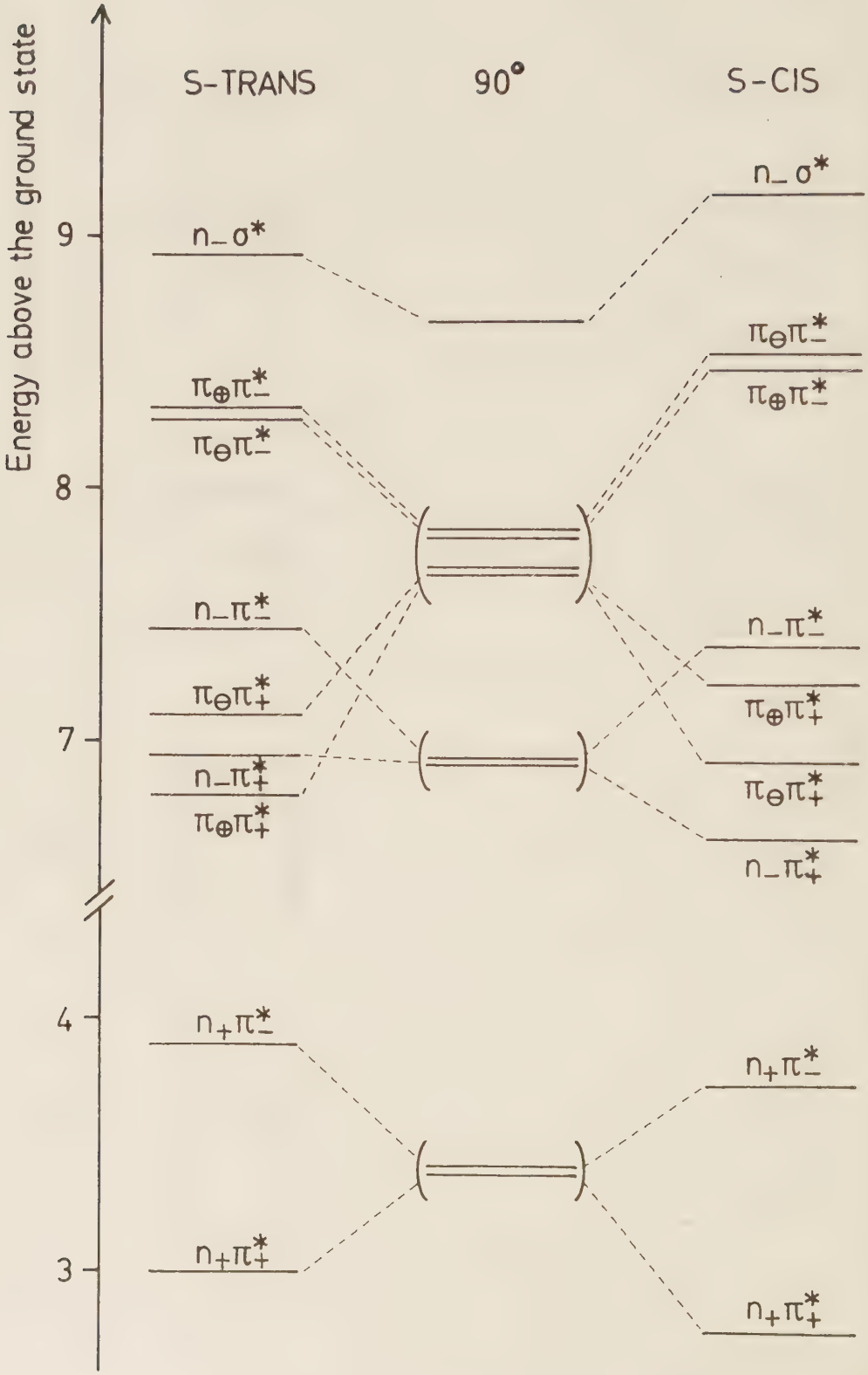
Figure 1. Vertical ionization potentials and assignments for the dithiooxamides and monothiooxamide VI.

Figure 2. Vertical ionization potentials and assignments for the monothiooxamides IV and V and for the component amides and thioamides.

Figure 3. UV absorption spectra in chloroform-cyclohexane (3:7 v/v) of a) I, b) IIa and c) IIc.



Scheme 1.


Energy above the ground state
S-TRANS
90°
S-CIS
9
8
7
4
3
n_σ*
π⊕π*_
π⊖π*_
n_π*_
π⊖π*+
n_π*+
π⊕π*+
n+π*_
n+π*+
n_σ*
π⊖π*_
π⊕π*_
n_π*_
π⊕π*+
π⊖π*+
n_π*+
n+π*_
n+π*+

Scheme 2.

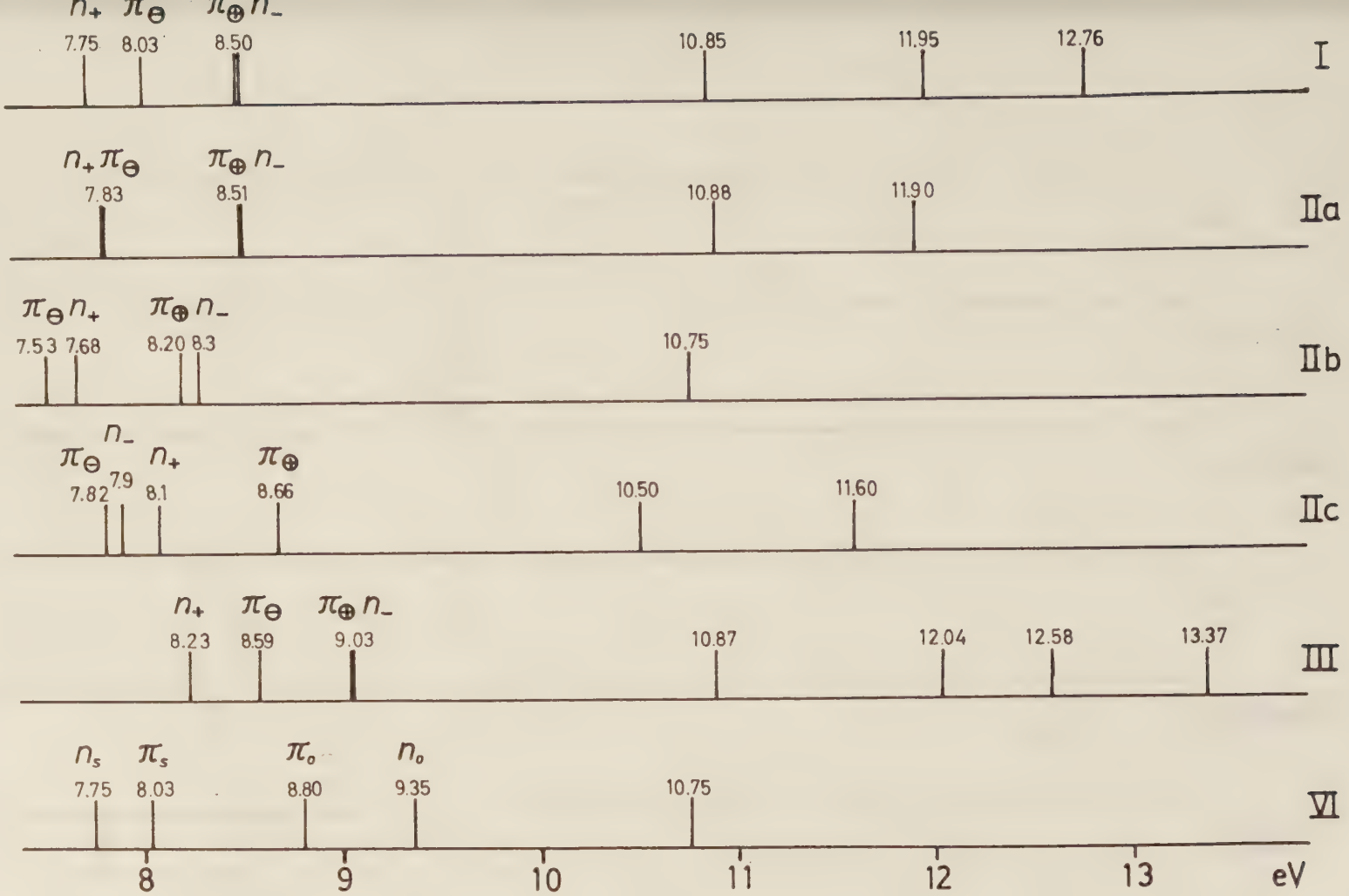

n+ π⊖ π⊕ n−
7.75 8.03 8.50 10.85 11.95 12.76
I
n+ π⊖ π⊕ n−
7.83 8.51 10.88 11.90
IIa
π⊖ n+ π⊕ n−
7.53 7.68 8.20 8.3 10.75
IIb
π⊖ n− n+ π⊕
7.82 7.9 8.1 8.66 10.50 11.60
IIc
n+ π⊖ π⊕ n−
8.23 8.59 9.03 10.87 12.04 12.58 13.37
III
ns πs πo no
7.75 8.03 8.80 9.35 10.75
VI
8 9 10 11 12 13 eV

Fig 1.

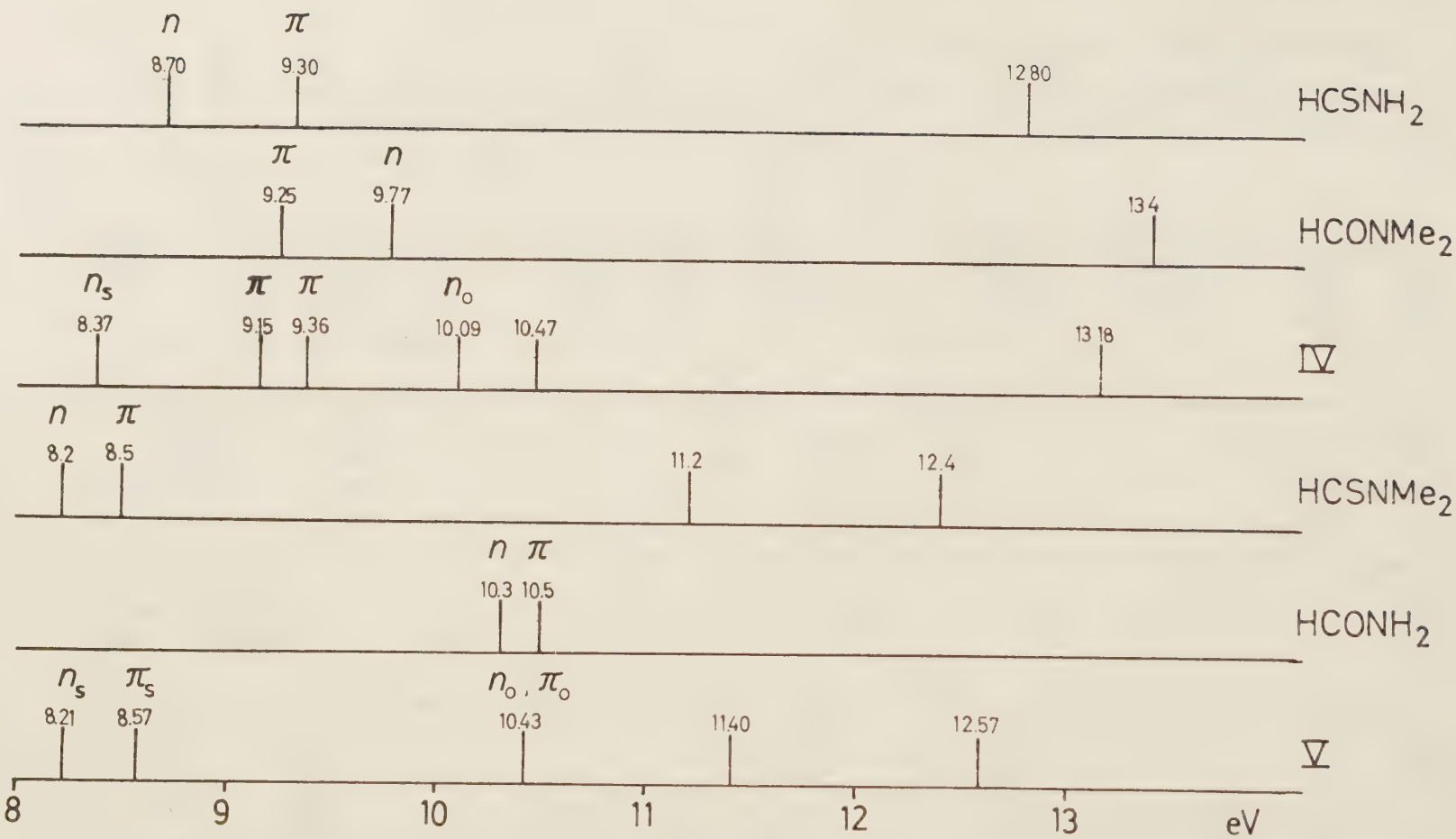

n
π
8.70
9.30
12.80
HCSNH2
π
n
9.25
9.77
13.4
HCONMe2
ns
π
π
no
8.37
9.15
9.36
10.09
10.47
13.18
IV
n
π
8.2
8.5
11.2
12.4
HCSNMe2
n
π
10.3
10.5
HCONH2
ns
πs
no , πo
8.21
8.57
10.43
11.40
12.57
V
8
9
10
11
12
13
eV

Fig 2.

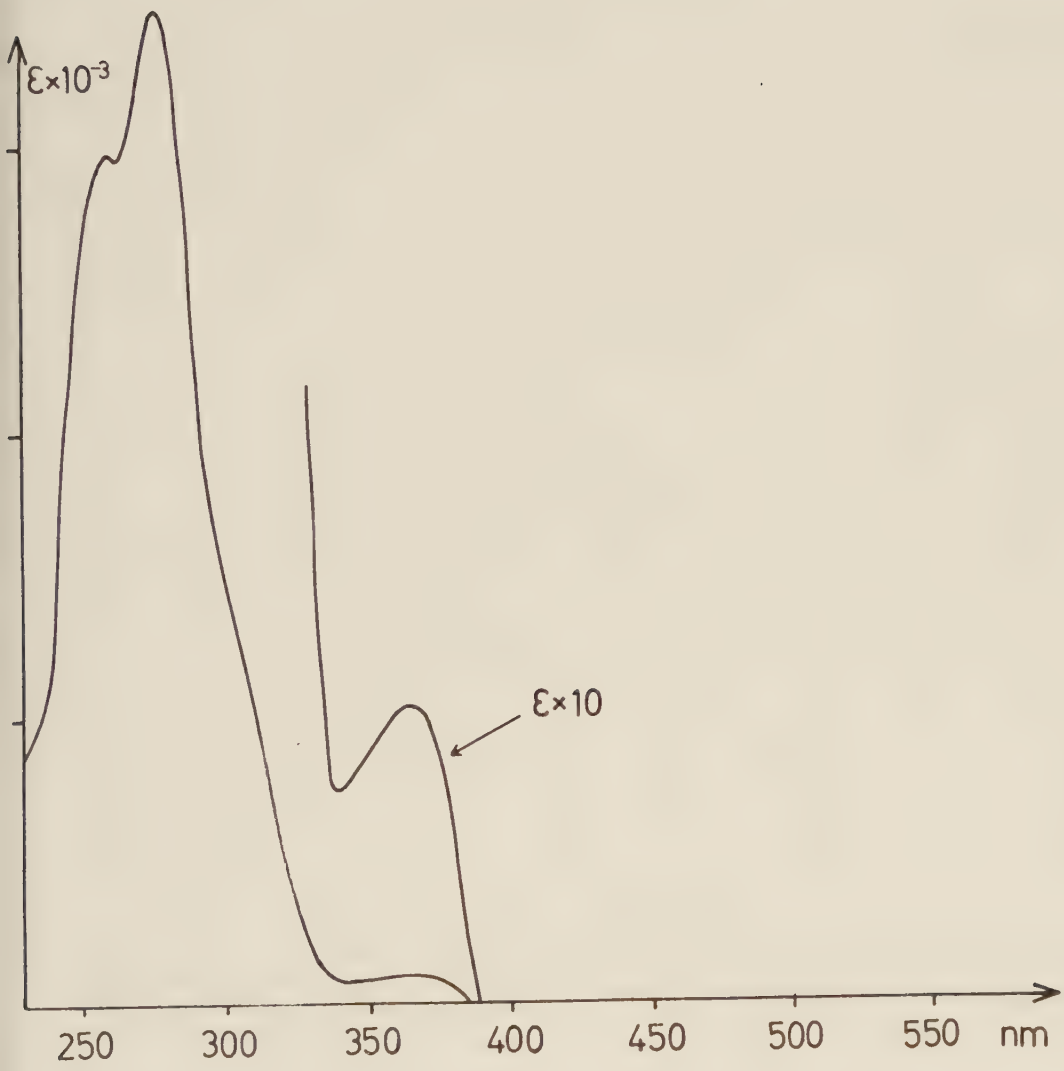


Fig. 3 a).

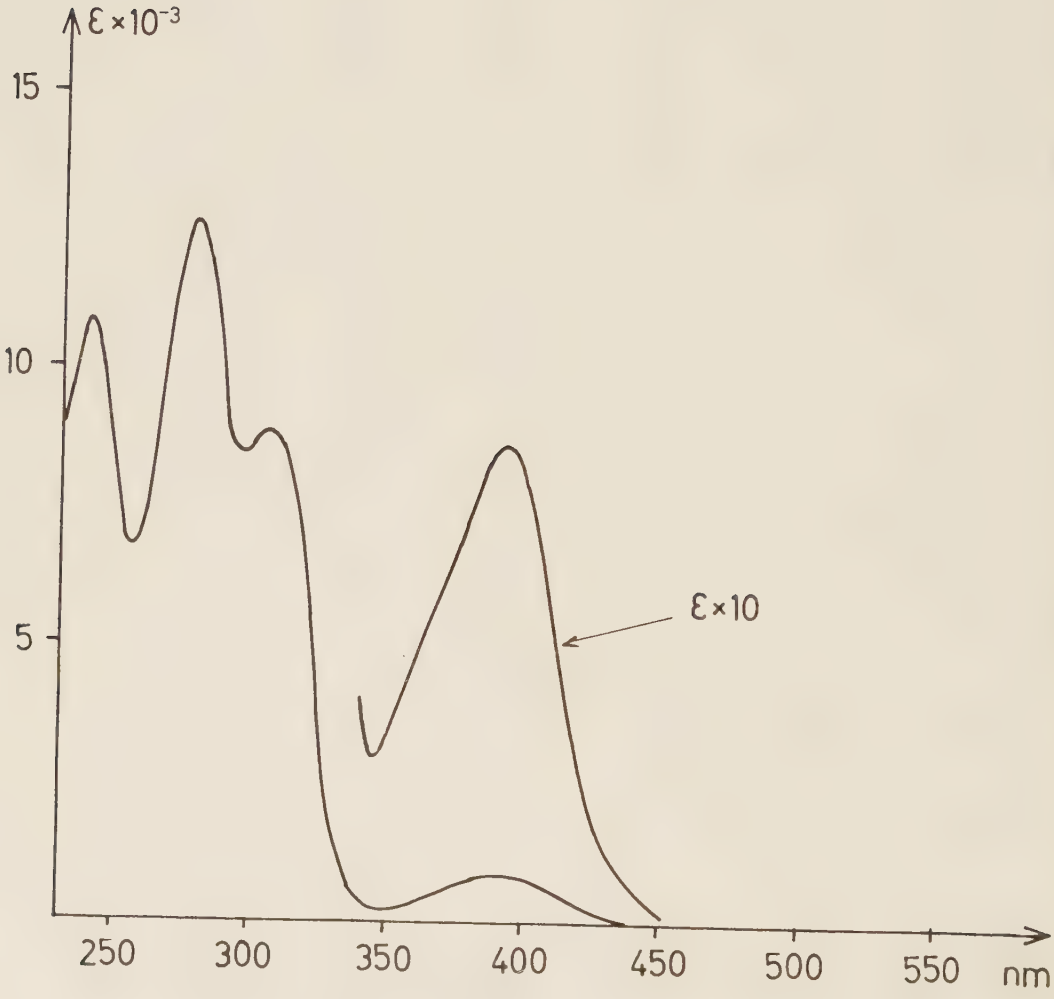


Fig. 3 b).

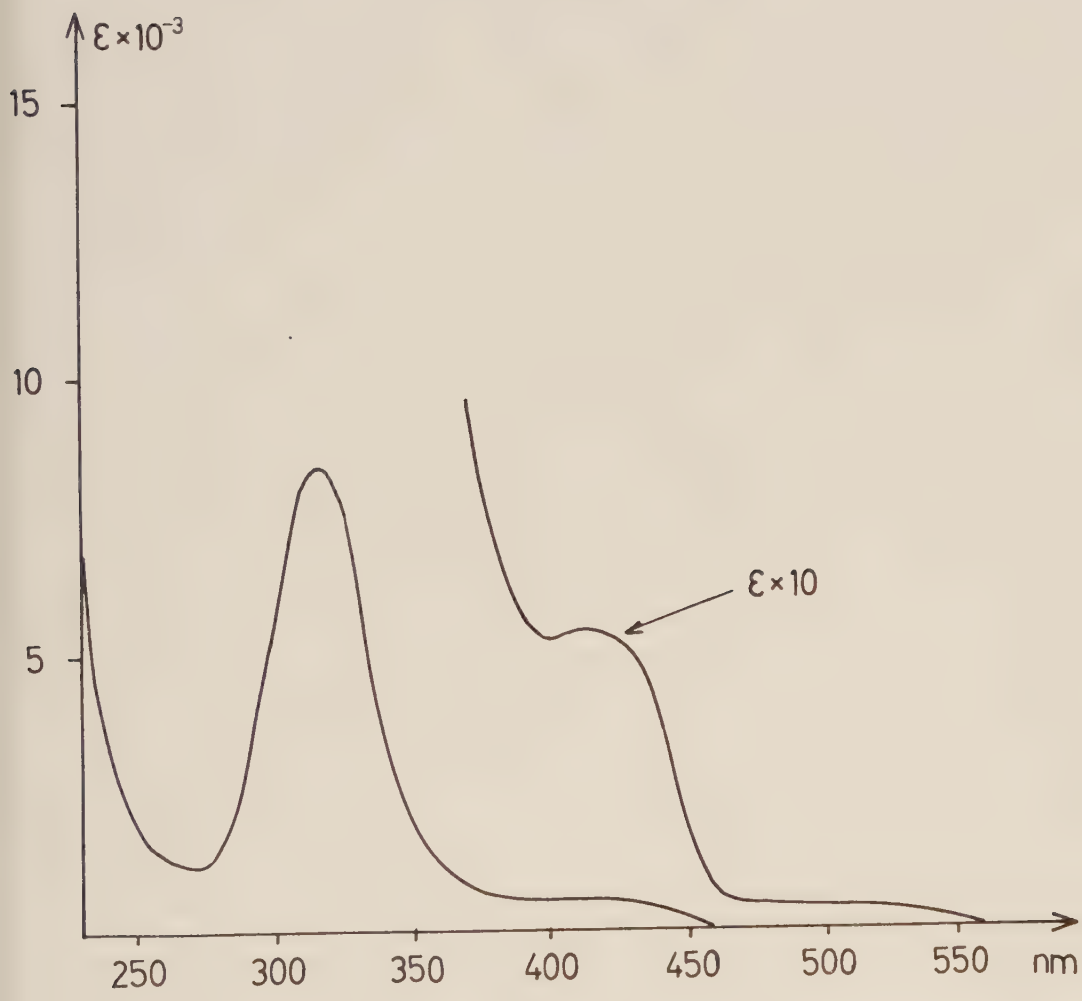


Fig. 3 c).

PAPER V

CONFORMATIONS AND BARRIERS TO INVERSION OF SOME CYCLIC SEVEN-MEMBERED α-DIKETONES. A STUDY BY DYNAMIC NMR SPECTROSCOPY AND MOLECULAR MECHANICS CALCULATIONS.

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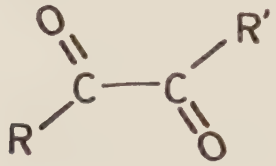
Abstract.

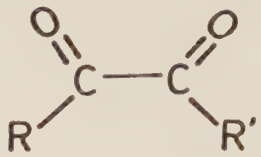
The dynamic stereochemistry of some seven-membered α-diketones have been studied by ^{1}H NMR spectroscopy and by molecular mechanics calculations. A force-field for α-dicarbonyl compounds has been developed. The cyclic α-diketones studied preferably adopt a distorted chair conformation with C_1 symmetry or a C_2 symmetric twist-boat conformation with a carbonyl-carbonyl dihedral angle of 90-114 degrees.
The inversion of the seven-membered ring system was interpreted in terms of a passage of the two carbonyl units in a planar s-cis conformation. The inversion barriers were found to be 8.6-10.8 kcal/mol with no significant entropy of activation.
Molecular mechanics calculations indicate that the electrostatic contribution to the inversion barrier is 36-58% of the total barrier heights.

INTRODUCTION

In α-dicarbonyl compounds, the dicarbonyl unit may exist in two planar conformations, s-cis and s-trans, both stabilized by π-conjugation.



s-trans



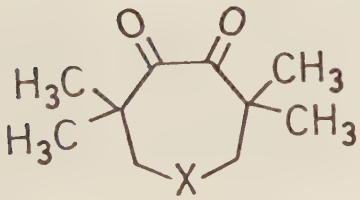
s-cis

Electrostatic repulsion between the carbonyl oxygens and repulsive steric interactions between the substituents R and R' should strongly disfavour the s-cis conformation. In acyclic aliphatic α-dicarbonyl compounds the s-cis conformation has only been observed for glyoxal[1], the simplest member of this class of molecules (R=R'=H). From the temperature dependence of the electronic spectrum of glyoxal an energy difference of 3.2 kcal/mol between the s-cis and s-trans conformations in favour of the latter was determined [2]. For methyl glyoxal[3] (R=H, R'=CH_3) and biacetyl [4,5] (R=R'=CH_3) only the s-trans conformation has been detected.

Much interest has been paid to the torsional potential and barrier to rotation around the carbonyl-carbonyl bond in simple α-dicarbonyl compounds. The great majority of the investigations, however, have exclusively had glyoxal as their object. A torsional potential function of glyoxal based on infra-red data and microwave intensities gives a rotational barrier of 5.06 kcal/mol at a dihedral angle of ca. 77° (s-cis = 0°).[6]

With the exception of the extensively studied glyoxal molecule, very few studies on the dynamic stereochemistry of aliphatic α-dicarbonyl compounds have been published. A Fourier analysis of the gas phase dipole moments of biacetyl at different temperatures resulted in a rotational barrier for this compound of 7.6 kcal/mol, with the s-cis structure as the transition state [7]. Further analysis of these data in combination with simple empirical calculations of non-bonded interactions gave a potential energy function with a maximum at a dihedral angle of ca 20°, 7.9 kcal/mol above the energy of the s-trans conformation. No significant barrier to rotation from the s-cis conformation was found. These studies on

biacetyl, however, suffer from the use of a rigid s-trans geometry in the calculations of non-bonded interactions and the conclusions, especially for the s-cis region, are therefore less reliable. Theoretical calculations on the conformational properties of α-diketones give widely different results depending on the calculational method used and/or the geometries assumed. MINDO/3 calculations on biacetyl using optimized geometries give an energy minimum at a dihedral angle of 105^0 and energy maxima for the s-cis and s-trans conformations, inconsistent with experimental data[9]. Ab initio calculations (STO-4G) using MINDO/3 geometries give energy minima for s-cis and s-trans with the s-trans conformation at 1.56 kcal/mol lower energy and with a low energy barrier to rotation, 2.53 kcal/mol, at a dihedral angle of 83°. Using the rigid rotor approach (s-trans geometry) STO-4G calculations give an energy difference between s-trans and s-cis of 4.42 kcal/mol in favour of the former. The rotational barrier is calculated to be 4.87 kcal/mol at a dihedral angle of 68°.[9] The potential energy function is thus calculated to be very shallow between 68° and 0°. A survey of the available investigations shows that, with the exception of glyoxal, reliable data on the dynamic stereochemistry of aliphatic α-dicarbonyl compounds are very scarce and that the properties of the s-cis conformation are largely unknown.
The present work was undertaken to obtain information on the changes in steric and electrostatic interactions with changes in the carbonyl-carbonyl dihedral angle in α-diketones. For this purpose the cyclic α-diketones I -V have been studied.

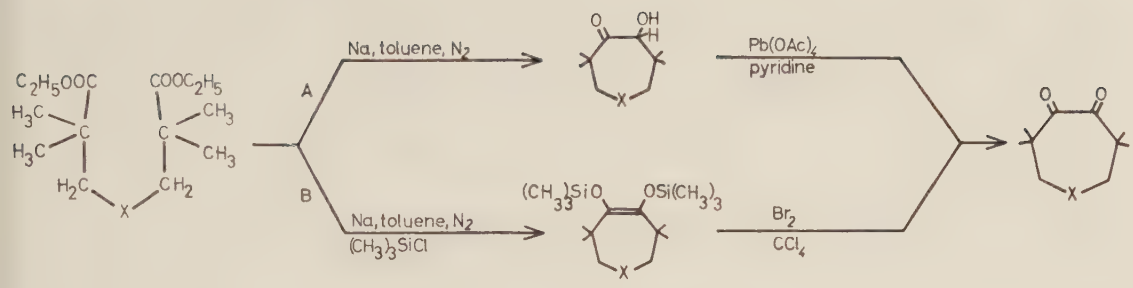


I X=CH_2
II X=O
III X=S
IV X=NCH_3
V X=$NC(CH_3)_3$

A study of the UV-spectra of I and some of its analogues with different ring sizes, indicates that the carbonyl-carbonyl dihedral angle in I is 90-110°.[10] The inversion of the seven-membered ring system should involve a passage of the two carbonyl groups in a planar or close to planar s-cis transition state, and the inversion barrier should reflect the electrostatic and steric interactions in this conformation. In the present work the inversion process was studied by dynamic ^{1}H NMR spectroscopy. The geminal methyl groups in I-V prevent enolization and also provide NMR signals whose temperature dependent bandshape could be conveniently used to evaluate rate constants for the inversion process. The substituents X in compounds II-V were introduced mainly to obtain geometrical variation of the ring system. As a bonus two isolated methylene groups are created whose NMR signals may be used to characterize the inversion process. To aid in the interpretation of the NMR-spectra and the observed inversion barriers, geometries and conformational energies was calculated by the molecular mechanics method. For this purpose a force-field for α-dicarbonyl compounds has been developed.

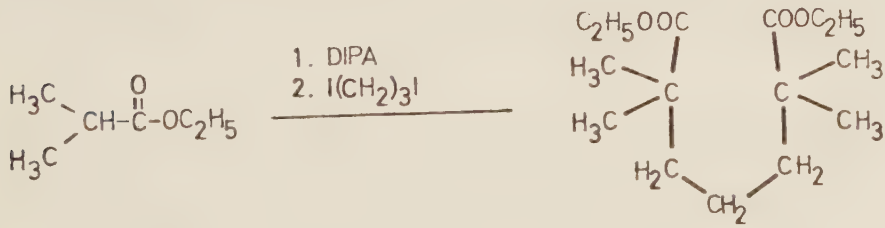
EXPERIMENTAL AND COMPUTATIONAL SECTION.

Materials. The compounds in this work were prepared by the acyloin condensation of the corresponding acyclic diesters and subsequent oxidation of the acyloins or disiloxenes, according to the methods described by Johnson[11] (Scheme 1).



Scheme 1.

Compounds III-V were prepared according to route A and I and II according to B. The final products were purified by thin layer chromatography. The diesters with X=S, NCH_3 and $NC(CH_3)_3$ were obtained as described by Wynberg[12] and Johnson[11]. New routes to prepare the diesters with $X=CH_2$ and O were developed. A synthesis of 1,1,5,5,-tetramethyl pimelate from phenyl isopropyl ketone and 1,3-dibromopropane has been described[10,13], but we found that the reaction between the anion of ethyl α-isobutyrate and 1,3-diiodopropane afforded the diester in a more convenient way.



The method used by Johnson[11] to prepare the diester with X=O involves the wellknown cancerogenous compound bischloromethyl ether. To avoid using this compound we prepared the diester via the Williamson ether synthesis. The yield was however poor.

Diethyl 1, 1,5,5 -tetramethyl pimelate. To a solution of 0.25 mol (25.1 g) of diisopropyl amine in 200 ml of dry ether was added 0.25 mol (16 g) n-butyllithium under nitrogen atmosphere at 0° C. To the reaction mixture was then dropwise added 0.25 mol (29 g) of ethyl α-isobutyrate in 100 ml dry ether. After stirring for two hours, allowing warming to room temperature during the last hour, 0.125 mol (25.5 g) of 1,3-diiodopropane was dropwise added. When the addition was completed the reaction mixture was refluxed for 12 hours and then cooled. To the reaction mixture was added 150 ml water. The organic layer was separated and dried with $MgSO_4$ and then distilled. Yield 18 g (53%), b.p 56-58° C /0.3 mm Hg, lit.[10] 105-106° C/1.3 mm Hg.

Diethyl 2,2,2', 2'-tetramethyl-3,3'-oxydibutanoate. To a mixture of 0.3 mol sodium hydride in 300 ml dioxane was added 0.1 mol (18.2g) bromopivalic acid [14] and 0.1 mol (11.8 g) hydroxypivalic acid [14] in 200 ml dioxane. A cathalytic amount of sodium iodide was added and the reaction mixture was refluxed for ca. 100 hours. The mixture was cooled on an ice bath and acidified with 50 % H_2SO_4. The reaction mixture was filtered and evaporated and the residue was recrystallized from acetic acid/petroleum ether (1:2). The yield of the diacid was 10 %. M.p 133-135° C.
The diester was obtained by refluxing 0.06 mol (12g) of the acid and 15 ml ethanol in 100 ml toluene in the presence of a cathalytic amount of para-toluenesulphonic acid. After the theoretical amount of water had separated (Dean Stark trap), the reaction mixture was cooled and washed with a sodium hydrogencarbonate solution. Destillation gave the diester in 80% yield, b.p. 73-76° C/0.1 mm Hg , lit.[15] 73-75° C/ 0.1 mm Hg.

NMR measurements. The ^{1}H NMR spectra were recorded on a JEOL Model JNM-MH-100 or a Bruker Model HX-270 NMR spectrometer. The samples were ca. 0.5 M solutions in $CHCl_2F$ or $(CD_3)_2CO$. Tetramethylsilane (TMS) was added to provide the internal lock signal. The temperatures were measured as described elsewhere.[16]
Rate constants were evaluated by visual fitting of experimental to calculated spectra for at least five temperatures around the coalescence temperature. The free energies of activation were obtained from the Eyring equation [17]. For III a complete bandshape analysis was performed using the combined rate constants obtained from the temperature depend-

ence of the geminal methyl signals and the ring methylene signals. The determination of the effective transverse relaxtion time (T_2) was performed as previously described.[18]

Molecular mechanics calculations. The calculations were performed using the MMP1 computer program developed by Allinger and coworkers.[19-21] In this program the effects of changes in π-conjugation on the geometry and conformational energy are taken into account.
The molecular mechanics scheme used in the MMP1 program have earlier been parametrized for conjugated hydrocarbons[19] and α,β - unsaturated aldehydes and ketones.[22] In the present work, the parametrization was extended to include α-dicarbonyl compounds. The force-field for α,β - unsaturated aldehydes and ketones was used as a starting point and it was found that only small corrections to the analogous parameters in this force-field were necessary to obtain a satisfactory force-field for α-dicarbonyl compounds. The parameters added to the MMP1 program are given in Table 1.
The geometry data used in the parametrization procedure were the electron diffraction geometries of s-trans glyoxal[23,24] and biacetyl[4,5] and (partly) the microwave geometry of s-cis glyoxal [25]. No attempt was made to fit the C-C and C=O bondlengths in the experimental s-cis geometry of glyoxal. The length of the C=O bond is generally assumed and it has been shown that the C-C bondlength strongly depends on this assumption.[25] Furthermore to be consistent with the parametrization in the MMP1 program, bondlength data obtained by diffraction techniques should be used. Unfortunately no electron diffraction geometry of s-cis glyoxal or biacetyl is available. Instead the needed slopes of the linear bond order-bond length and bond order-force constant relations were assumed to be the same as for α,β-unsaturated aldehydes and ketones.[22] Experimental and calculated geometries for s-trans and s-cis glyoxal and biacetyl are given in Table 2.

The torsional V_2 term was evaluated by fitting the calculated rotationa barrier for glyoxal to the experimental one.[6] The potential energy function thus obtained gives an energy difference between the s-cis and s-trans conformations of 3.59 kcal/mol in good agreement with experiments, 3.2 ± 0.6[2] and 3.37 ± 0.43 kcal/mol.[6]
Extending the calculations to biacetyl a rotational barrier of 5.5 kcal/mol at a dihedral angle of 40° was calculated. The s-cis conformation was calculated to be 5.37 kcal/mol higher in energy than the s-trans conformation. In agreement with ab initio calculation[9] and the potential energy function obtained from dipole moment data[8], the potential energy does not show any significant changes in the dihedral angle interval 40°-0°. The calculated barrier to rotation for biacetyl is ca. 2 kcal/mol lower than was obtained from dipole moment data.[7,8] This is to be expected since our calculated barrier corresponds to fully energy-minimized geometries, while the dipole moment data were interpreted using a rigid dicarbonyl geometry.
The molecular mechanics calculations described above all use the dipole-dipole approximation to calculate the electrostatic interactions. As this approximation is somewhat doubtful for dipoles at close distance, we have also used coulombic charge-charge interactions in the calculations. The atomic partial charges used were obtained from ab initio calculations and are given in Table 1. Using these charges the calculated rotational barrier for biacetyl becomes 6.01 kcal/mol. In all calculations an effective dielectric constant of 1.5 was employed.[27]

RESULTS AND DISCUSSION.

Variable temperature NMR spectra. Ambient temperature ^1H NMR spectra of compounds I-V all display a sharp singlet for the four methyl groups. At lower temperatures this signal broadens and finally I-IV splits into a doublet. For compound I this splitting could only be observed in the 270 MHz spectrum, due to a small shift and line broadening at the low temperatures required. For compound V no splitting of the methyl resonance signal was observed. This is probably due to a very small shift and also to interfering overlap by the $N-C(CH_3)_3$ signal. Compounds II- V have two isolated ring methylene groups which give rise to a sharp singlet at ambient temperature and in II, III and V an AB pattern below coalescence. In the low temperature spectrum of IV a small shift and strong overlap by the NCH_3 signal precluded the analysis of the methylene signals. No temperature dependence of the N-substituent signals was observed. Coalescence temperatures and chemical shifts and coupling constants at slow exchange are given in Table 3.

The AB shifts and also the methyl group shifts vary considerably through the series of compounds. This variation may be attributed to the different magnetical anisotropies of the ring hetero substituents. The geminal coupling constants for the methylene groups in II, III and V decrease, as expected, numerically with increasing electronegativity of the hetero atom substituent.

Rate constants were evaluated from the temperature dependent band shapes as described in the experimental section. Free energies of activation were calculated using the Eyring equation. The energy data obtained are given in Table 4.

For compounds II and III it was possible to study the temperature dependence of two different sets of proton signals arising from the methyl and methylene groups, respectively, The free energies of activation obtained from the two sets of rate constants were identical within error limits, indicating that the temperature dependence of the NMR spectrum corresponds to only one dynamic process.

For III a total band shape analysis was performed using the combined sets of rate constants. The activation entropy obtained does not significantly deviate from zero (cal/mol.deg).

Conformations. The compounds studied in this work may formally exist in a large number of conformations of the chair/twist-chair or boat/twist-boat families, in analogy with the different conformations in the pseudorotational scheme of cycloheptane as analyzed by Hendrickson.[31] However, repulsive steric interactions between the two sets of geminal methyl groups and also electrostatic repulsion between the two carbonyl groups drastically reduce the number of low energy conformers.

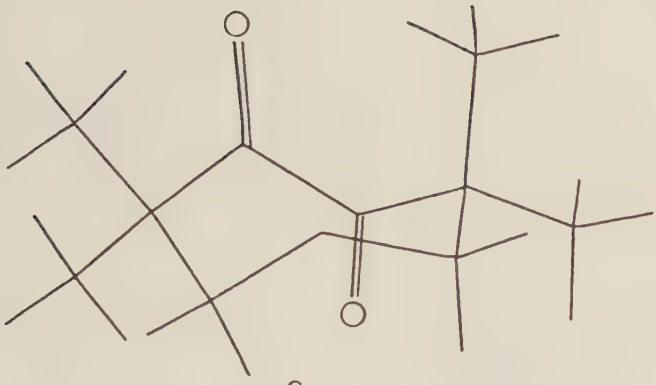
The NMR data described above are only consistent with conformations having C_2 or C_s symmetries, possibly time averaged, with the C_2 axis or the mirror plane bisecting the carbonyl groups. The C_s symmetry is less probable, since it requires eclipsing of the two carbonyl groups, maximizing the repulsive electrostatic interaction between the two oxygens. Furthermore, a carbonyl-carbonyl dihedral angle of 0° (s-cis) is inconsistent with UV data from which a dihedral angle of $90\text{-}110^{\circ}$ has been infered.[10]

Molecular mechanics calculations, performed as described in the computational section, indicate that only a small number of low energy conformers are present. An extensive search of the potential energy surface using several different trial input geometries resulted in the location of two low energy local minima. The corresponding conformations are C_2 twist-boat and a slightly distorted chair conformation with C_1 symmetry. The computer generated geometries of these conformations are shown in Fig 1. The corresponding conformational energies for compounds **I**-**V** are given in Table 5.

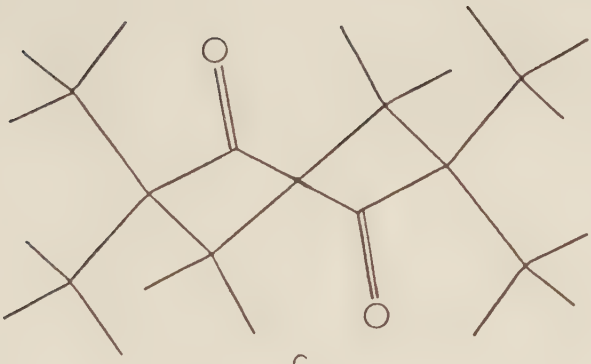
For **II**-**V** the C_1 conformer is calculated to be the prefered one. For **I** the C_2 twist-boat is of lowest energy with the C_1 conformation at ca. 1 kcal/mol higher energy.

In both conformations the carbonyl-carbonyl dihedral angle is calculated to be in the interval $90\text{-}114^{\circ}$ in agreement with conclusions from UV data.

Inspection of the calculated geometry of the twist-boat conformer of **I** shows that the bond lenghts and bond angles for the C-CO-CO-C fragment are very close to the corresponding geometrical parameters calculated for biacetyl using the same dihedral angle. This means that compound **I**, as far as the dicarbonyl unit is concerned, may serve as an accurate model for a $\sim 100^{\circ}$ twisted biacetyl molecule.



C_1



C_2

Fig.1.

The calculated preference for the C_1 structure in compounds II-V is at first glance at variance with the NMR data of these compounds at slow exchange (see Table 3). A C_1 symmetry should lead to four different methyl signals and two AB quartets in the NMR spectra below the coalescence temperature.
However, pseudorotation provides a low energy path for pairwise exchange of the methyl groups and methylene protons in the C_1 conformation, resulting in pairwise time averaged methyl and methylene shifts in accordance with the number of signals observed in the low temperature NMR spectra.
The scheme for the exchange is shown in Fig. 2.
The free energy of activation for this pseudorotational process is too low to allow the process to be observed in the temperature dependent NMR spectra.

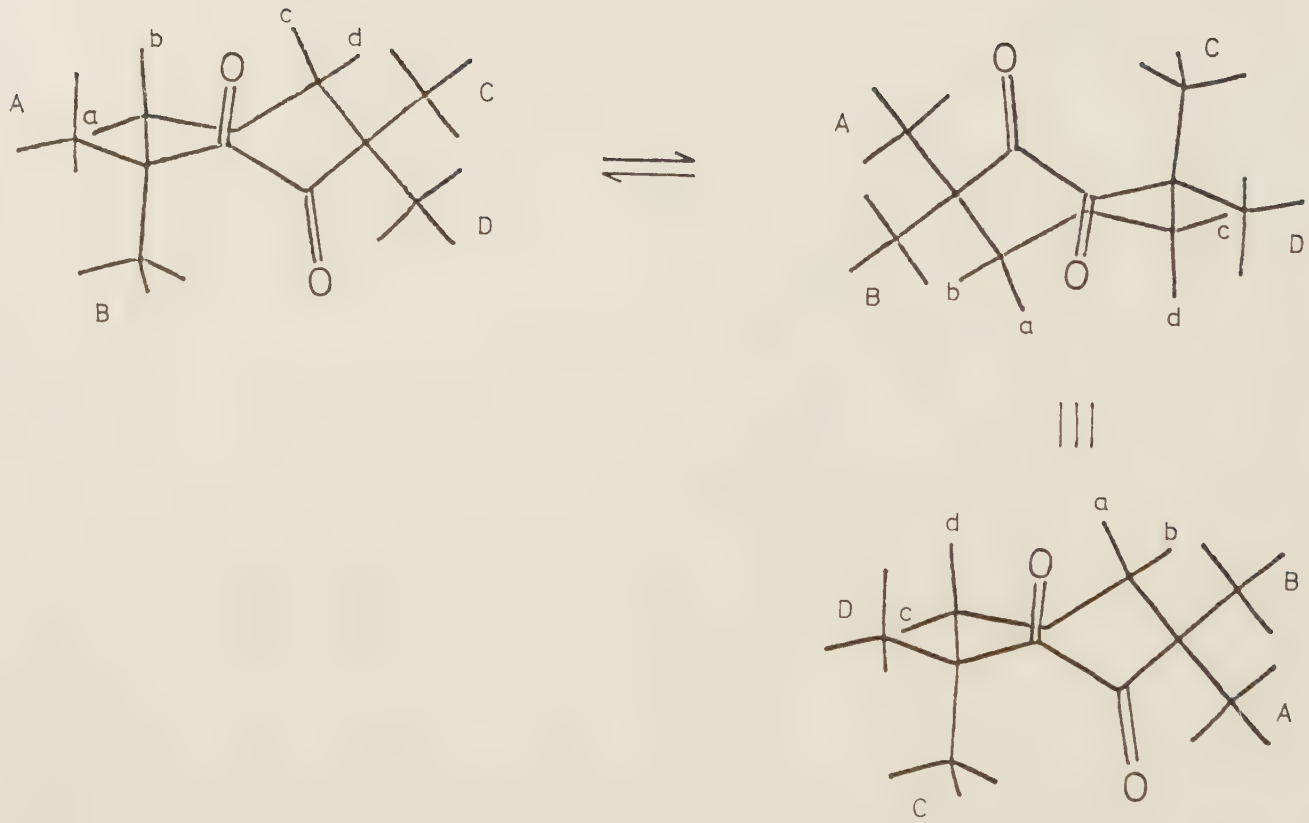
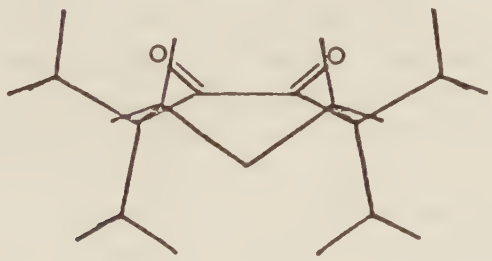


Fig.2.

Barriers to inversion. The free activation energies to inversion of the seven-membered ring system in I-V, given in Table 4, show only a small dependence of the barrier on the ring hetero substituent in II, IV and V. The introduction of a sulphur atom in II, however, gives an increase in the barrier of ca. 2 kcal/mol when compared to the barrier of I.

Using the molecular mechanics method a suitable transition state structure for the inversion process was searched for, with the aid of the pseudorotational map of cycloheptane.[31] The inversion process in I-V requires a passage of the carbonyl groups and as this corresponds to a dicarbonyl arrangement with maximum repulsive electrostatic interaction between the two carbonyl oxygens, it was considered reasonable to assume an s-cis or close to s-cis conformation of the dicarbonyl unit in the transition state for the inversion process. The lowest energy s-cis geometry found a C_s chair conformation, is shown below.



C_s

The corresponding C_s boat was calculated to be of ca. 5 kcal/mol higher energy. Several pathways are, however, available for a (twist),boat/ (twist)-chair interconversion which do not require an eclipsing of the carbonyl groups.

By calculating the conformational energy of the C_s chair conformer as a function of small stepwise changes of the CO-CO dihedral angle, this structure was shown to be a local energy maximum on the potential energy surface.

The calculated inversion barriers are given in Table 6, which also shows the calculated electrostatic contributions to the total barrier, using two models for the calculation of the electrostatic interactions.

The overall agreement between calculated and experimental barriers (Table 4) is quite satisfactory, the most significant differences being an overestimation of the barriers in I and III. For more accurate calculations on these strongly polar molecules a better description of the charge distribution, including all atoms, is probably required.

Surprisingly no significant difference in the calculated barriers using the two electrostatic models were found.

The calculated transition state geometries for I-V indicate that the inversion process is accompanied by large changes in bond angles for the dicarbonyl unit. The C-CO-CO angle is increased by ca. 12°, while the two C-C-O angles are decreased by 4° and 8° respectively. These angle bendings make up a significant part of the calculated steric contribution to the inversion barrier. The changes in bond angles are significantly different from those calculated for biacetyl. In this molecule the changes are + 2°, + 1.5° and - 3.3°, respectively, on going from a dihedral angle of 100° to 0° (s-cis). Thus, the ring system and the presence of geminal methyl groups on the ring forces the carbonyl oxygens to come closer to each other in the C_s chair transition state structure of I-V than is the case in the s-cis conformation of biacetyl. As a consequence the electrostatic part of the inversion barriers in I-V, 3.9-5.0 kcal/mol (Table 6) is significantly larger than is calculated for the corresponding dihedral angle change in biacetyl, 2.9 kcal/mol. Thus, while the prefered conformation of I was found to be an accurate model for biacetyl with a dihedral angle of ca. 100° the s-cis chair conformation is appreciably different in geometry when compared to s-cis biacetyl.

The electrostatic part of the barrier to inversion in I-V is calculated to be 36-58% of the total barriers. This is much larger than was found for the inversion of seven-membered cyclic oxamides which were calculated to have initial and transition state geometries in an overall simlarity to those calculated for I-V. The electrostatic contributions to the inversion barrier of the oxamides was calculated to be only 7-11%.[32] One reason for this difference is to be found in the different CO-CO dihedral angles in the lowest energy conformation.

For the oxamides this was calculated to be only ca 60°, resulting in a sizeable electrostatic repulsion already in the initial state of the inversion process of the seven-membered ring system.

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Table 1 Force field parameters[a].

Natural Bond Lengths and Stretching Force Constants.

Bond	l_o,Å	Slope(l_o)[b]	k_l,mdyn/Å	Slope(k_l)
$C_{co}-C_{co}$[c]	1.366	0.179	9.60	4.60

Natural Bond Angles and Bending Force Constants.

Angle	θ_o, deg	k_θ,mdyn.Å/rad^2
C_{co}-C=O	121.0	0.50
$C_{sp^3}-C_{co}-C_{co}$	113.0	0.40
$H-C_{co}-C_{co}$	113.0	0.40

Torsional constants.

Angle	V_2,kcal/mol	V_3,kcal/mol
$X-C_{co}-C_{co}-Y$[d]	9.42	
$H-C_{sp^3}-C_{co}-C_{co}$		-0.75
$C_{sp^3}-C_{sp^3}-C_{co}-C_{co}$		-0.33

Bond Moment

Bond	μ,D
C=O	2.90

Table 1. (cont.)

Fractional atomic charges.

Atom	Charge	Ref.
C=$\underline{O}$	-0.44	28
$\underline{C}$=O	+0.34	28
$\underline{C}$-C_{co}	+0.10	28
C-$\underline{N}$<C C	-0.30	29
C-$\underline{O}$-C	-0.28	29
C-$\underline{S}$-C	-0.13	30
$\underline{C}$-N	+0.10	29
$\underline{C}$-O	+0.14	29
$\underline{C}$-S	+0.06	30

[a] For notations see ref.19 and 20.

[b] These are slopes defining linear bond order-bond length and bond order-force constant relations[19].

[c] C_{co}=carbonyl carbon.

[d] X,Y=O, H or C_{sp} 3

Table 2 Calculated and experimental geometries for s-trans and s-cis glyoxal and biacetyl.

Bond (Å) / Angle (deg)	Glyoxal				Biacetyl		
	s-trans		s-cis		s-trans		s-cis
	calc.	exp.[23,24]	calc.	exp.[25,26]	calc.	exp[5]	calc
$C_{co}-C_{co}$	1.527	1.525,1.526	1.529	1.514	1.528	1.531	1.535
C=O	1.215	1.208,1.212	1.217	1.207 (ass)	1.218	1.215	1.221
$C_{co}-H$	1.112	1.119,1.132	1.113	1.130			
$C_{co}-CH_3$					1.509	1.517	1.513
$C_{co}-C_{co}=O$	120.9	121.6	124.6	123.4,123.8	119.5	119.5	121.1
$C_{co}-C_{co}-H$	116.0	115.4	115.3	116.2,115.5			
$C_{co}-C_{co}-CH_3$					116.5	116.6	118.2
H-C=O	123.1	123.0	120.0	120.4,120.7			
$CH_3-C=O$					124.0	123.9	120.7
Dipolmoment (D)			4.77	4.8[1]			

Table 3. ^{1}H NMR data at slow exchange.

Compound	Signals studied	Solvent	Temp (k)	T_c(k)	$\Delta\nu$(Hz)	J_{AB}(Hz)
I	$C\underline{H}_3$	$CHCl_2F$	168	173	19.5 [a]	
II	$C\underline{H}_3$	$CHCl_2F$	164	169	26.2	
II	$C\underline{H}_2$	$CHCl_2F$	164	173	44.7	13.0
III	$C\underline{H}_3$	$(CD_3)_2CO$	178	200	3.8	
III	$C\underline{H}_2$	$(CD_3)_2CO$	212	217	21.5	14.3
IV	$C\underline{H}_3$	$CHCl_2F$	173	183	23.0	
V	$C\underline{H}_2$	$CHCl_2F$	172	188	82.9	13.8

[a] 270 MHz spectrometer.

Table 4. Free energy barriers to inversion for compounds I-V

Compound	Signals studied	$\Delta G^{\#}$ (kcal/mol) [a]	Temp. (K)
I	CH_3	8.7	168.0
II	CH_3	8.6	171.1
II	CH_2	8.6	171.1
III	CH_3	10.8 [b]	171.0
III	CH_2	10.8 [b]	211.9
IV	CH_3	9.1	181.4
V	CH_2	9.3	186.0

a) estimated error ± 0.1 kcal/mol

b) $\Delta H = 10.8 \pm 0.1$ kcal/mol
$\Delta S = -0.1 \pm 0.3$ cal/mol.deg

Only random errors calculated from the standard deviations in the Eyring plot are included.

Table 5. Calculated conformational energies[a] and carbonyl-carbonyl dihedral angles for compounds I-V

Compound	C_1 conformation (kcal/mol)	CO-CO dihedral angle (deg.)	C_2 twist-boat (kcal/mol)	CO-CO dihedral angle (deg.)
I	+ 1.05	103.8	0	94.5
II	0	99.6	+ 0.33	89.7
III	0	114.8	+ 0.82	105.4
IV	0	101.0	+ 0.57	92.1
V	0	100.1	+ 4.18	90.4

[a] dipole approximation.

Table 6. Molecular mechanics calculated inversion barriers[a] for compounds I-V

Compound	Dipole-dipole model		Charge-charge model	
	calc.barrier	electrostatic part	calc. barrier	electrostatic part
I	10.6	3.9	10.8	3.9
II	7.7	4.4	7.9	4.6
III	11.7	4.9	11.8	5.0
IV	8.6	4.2	8.8	4.4
V	8.4	3.9	8.8	4.3

a) energies in kcal/mol